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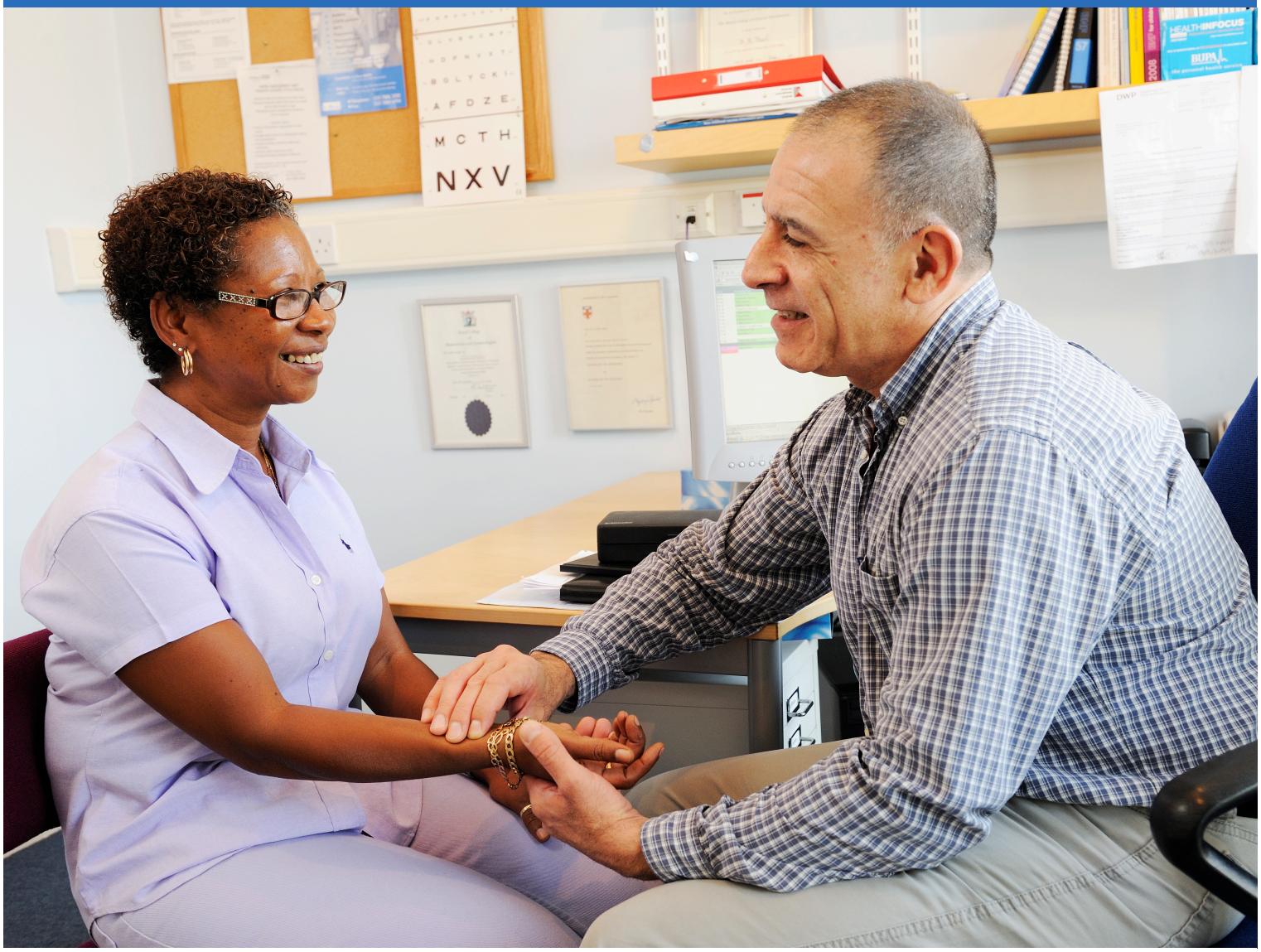
Evaluation of cranial nerve mononeuropathy

Straight to the point of care



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Summary

Cranial nerve mononeuropathies present with varying signs and symptoms depending on which nerve is affected. The effects of the mononeuropathy also depend on where in its pathway the nerve is affected, and the etiology.

There are 12 paired cranial nerves, named and numbered according to the rostral-caudal order of attachment to the brain. They serve a variety of functions and predominantly provide the motor and sensory innervation to the head.

Olfactory (I)

Anatomy

Olfaction begins with transduction of odorants from the air into the nasal mucosa. These odorants diffuse or are transported to bipolar receptor cells located in the olfactory neuroepithelium in the roof of the nasal chamber. Action potentials are induced in these cells, which synapse with olfactory bulb glomeruli.[1] The receptor cell axons project through the cribriform plate of the ethmoid bone and synapse within the glomerular layer of the olfactory bulb. The paired olfactory bulbs are located at the base of the frontal lobe overlying the cribriform plate.[2] The second-order neurons leave the olfactory bulb to synapse on the primary olfactory cortex. These areas encode characteristics of odor quality, identity, familiarity, and emotion.[3]

Function and disorders

Changes in olfactory function frequently go unnoticed and often do not present to a clinician.[2] Patients may notice altered taste, rather than a loss of sense of smell.[4] Olfaction is critically important for safety, nutritional status, and quality of life. Disorders can manifest as a total loss of smell (anosmia), partial loss of smell (hyposmia), distortions (dysosmias), or spontaneous olfactory hallucinations (phantosmias).[2] Infrequently, olfactory dysfunction can be the presenting sign/symptom of neurodegenerative disorders (such as idiopathic Parkinson disease), or an intracranial mass lesion.

Nerve testing

The diagnosis can usually be made clinically. Commercial odor identification tests are available, which require patients to identify several predefined smells.[5] These may be useful to confirm olfactory dysfunction. Psychophysical tests are useful to validate and classify olfactory dysfunction, but establishing the cause of olfactory loss relies heavily on the history. Olfactory evoked potentials are available in specialist centers.

Optic (II)

Anatomy

Axons making up the optic nerve arise from retinal ganglion cells. These axons run toward the lamina cribrosa and merge in the optic papilla. At this point, they form the optic nerve. In the orbital apex, the nerve passes through the extraocular muscle origins and enters the optic canal. The nerve continues to course upward and inward until it meets with the contralateral nerve to form the optic chiasm superior to the sella and pituitary gland.[6] Action potentials are then carried to the lateral geniculate body. The intraorbital portion

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is surrounded by the subarachnoid space and dura that extends from the intracranial cavity. The central retinal artery and vein course through the middle of the nerve.

Function and disorders

Humans have a highly developed visual system, which transmits information from the environment. The optic nerve carries millions of fibers from the retina into the central nervous system (CNS).[7] Vision is critical for human function and, as such, optic nerve pathology can severely affect quality of life.[6] Optic nerve lesions typically produce monocular visual loss, which can be sudden or gradual, and may or may not be associated with pain. The potential causes of optic neuropathy are diverse and include vascular, toxic, metabolic, traumatic, compressive, infectious, inflammatory, and idiopathic etiologies.

Nerve testing

Symptoms of optic nerve damage can represent changes in visual acuity, contrast, brightness, or colour.[6] A detailed description of visual dysfunction is essential and can narrow the differential. To define the degree of optic nerve dysfunction, the following tests are frequently performed.

- Visual acuity: tested using a Snellen chart.[4] Optic nerve damage may result in central visual loss.
- Color vision: assessed with a series of color plates. Patients with unilateral optic nerve impairment have difficulty identifying colors (dyschromatopsia); color perception is more likely to be significantly affected than visual acuity.
- Pupillary testing: pupillary light reflex testing for relative afferent pupillary defect (RAPD) is the only bedside test of optic nerve dysfunction that is independent of patient's subjective response.[6]
- Visual fields testing: a basic visual field test can be performed at the bedside by comparing the patient's peripheral vision with the clinician.[4] If a defect is identified, formal testing may be required, for example with Goldmann perimetry. The more central part of the visual field may be tested using an Amsler grid.
- Direct ophthalmoscopy: visualizing the optic nerve as it enters the back of the eye can reveal pallor (optic atrophy) or disk swelling (papillitis or papilledema).
- Electrodiagnostic testing: visual evoked potentials (VEPs) can be performed to objectively assess for conduction slowing at the optic nerve. This potential is recorded from surface electrodes on the scalp while displaying visual patterns or light flashes to either eye. Note that visual pathway lesions posterior to the optic chiasm are technically more challenging to identify with VEP.[8]

Oculomotor (III), trochlear (IV), and abducens (VI)

Anatomy

- The oculomotor nerve emerges from the midbrain nucleus that lies ventral to the sylvian aqueduct. One unpaired and 4 paired subnuclei can be distinguished. The most dorsal subnucleus contains the visceral Edinger-Westphal nucleus and the levator palpebrae nucleus. The Edinger-Westphal nucleus mediates pupillary constriction. Laterally the dorsal, intermediate, and ventral subnuclei provide innervation to the ipsilateral inferior rectus, inferior oblique, and medial rectus, respectively. The oculomotor nerve fascicles leave the nucleus and pass ventrally through the red nucleus before exiting just medial to the cerebral peduncles. In the subarachnoid space the third nerve passes between the superior cerebellar and posterior cerebral arteries. The nerve then enters the lateral wall of the cavernous sinus and divides into a superior and inferior branch as it enters the orbit through the

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superior orbital fissure.[9] The oculomotor nerve contains inner somatic nerve fibers innervating the extraocular muscles, surrounded by outer autonomic nerve fibers mediating pupillary constriction.[10]

- The trochlear nucleus is located in the midbrain tegmentum at the level of the inferior colliculus. The nerve fascicles course posteroinferiorly to decussate at the anterior medullary velum before exiting from the dorsal aspect of the midbrain. The trochlear nerve is the only nerve to arise from the dorsal aspect of the brainstem. The fourth nerve traverses the brainstem cisterns close to the undersurface of the tentorial edge and pierces the dura to enter the lateral cavernous sinus. The trochlear nerve enters the orbit through the superior orbital fissure to innervate the superior oblique muscle.[9]
- The abducens nucleus contains motor neurons for the lateral rectus and interneurons traveling through the medial longitudinal fasciculus to the contralateral third nerve nucleus (to allow simultaneous movement of the contralateral medial rectus muscle). The nerve fascicles leave the nucleus and travel within the pontine tegmentum to leave the brainstem in the horizontal sulcus between the pons and medulla. The nerve enters the subarachnoid space and courses vertically along the clivus over the petrous apex of the temporal bone, where it is tethered in the Dorello canal. It then enters the cavernous sinus lateral to the internal carotid artery and finally enters the orbit through the superior orbital fissure.[9]

Function and disorders

- The third, fourth, and sixth cranial nerves are responsible for eye movements.
- The third cranial nerve controls most extraocular muscles, including the superior, inferior, and medial recti, and the inferior oblique muscles. In addition, it innervates the levator palpebrae superioris, which elevates the eyelid, and carries parasympathetic innervation to the pupil. Patients often present with paralysis of adduction, elevation, and depression, and when the pupil is involved a large unreactive pupil is noted. This presentation can suggest serious neurologic disorders, namely subarachnoid hemorrhage, cerebral aneurysms, uncal herniation, or meningitis. Prompt recognition and evaluation is needed.
- The fourth cranial nerve innervates the superior oblique muscle, which controls depression, intorsion, and adduction of the eye. It is the most common cause of vertical diplopia. The frequency of fourth nerve palsy is difficult to accurately report, but in one large series it was more common than both oculomotor and abducens palsies.[11] [12] The abducens nerve innervates the lateral rectus muscle and controls abduction. Patients typically present with horizontal double vision. It may be an isolated finding or part of a systemic disease.[9]

Nerve testing

Simple bedside testing of eye movements can be performed to elicit a third, fourth, or sixth nerve palsy. The patient is asked to keep his or her head still and follow the examiner's index finger with the eyes. The examiner slowly moves his or her finger up and down and from side to side at eye level and observes eye movements.[4] The patient should report back any diplopia. Diplopia is maximal in the direction of action of the paralyzed muscle. Of the duplicated images perceived by the patient, the image seen in the periphery is perceived from the paretic (abnormal) eye and should disappear upon occlusion of the eye.[4]

Trigeminal (V)

Anatomy

The trigeminal nerve has 3 main branches: ophthalmic (V1), maxillary (V2), and mandibular (V3).[13] V1 enters the cranial cavity through the superior orbital fissure, V2 through the foramen rotundum, and V3 through the foramen ovale. V1 and V2 traverse the cavernous sinus. The first-order cell bodies carrying

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modalities of pain, temperature, pressure, and light touch in all 3 branches are located in the trigeminal (gasserian) ganglion in the Meckel cave (near the petrous apex of the temporal bone). Proprioceptive fibers have their first-order cell bodies in the mesencephalic nucleus of the brainstem. From the trigeminal ganglion, the nerve fibers enter the pons and synapse in multiple trigeminal nuclei. From there, second-order neurons carry afferent information to the ventral posteromedial nucleus of the thalamus. Finally, third-order neurons relay to the primary sensory cortex. Efferent motor fibers originate in the motor nucleus of the trigeminal nerve in the midpons and travel with V3 through the foramen ovale to supply the muscles of mastication (masseter, temporalis, mylohyoid, medial and lateral pterygoid, and anterior belly of the digastric), as well as the tensor tympani and tensor veli palatini. The trigeminal nerve and its branches also mediate the afferent limbs of the corneal blink and lacrimal reflexes, and both afferent and efferent limbs of the jaw-jerk reflex.

Function and disorders

The trigeminal nerve is the largest cranial nerve.[4] It carries sensation from the face and mucosal surfaces, cornea, and supratentorial dura, as well as providing motor innervations to the muscles of mastication. The differential diagnosis for trigeminal neuropathy is very broad. Intra-axial pathology, particularly of the pons, can result in trigeminal dysfunction, but only rarely does this result in a mononeuropathy. Extra-axial lesions are more likely to affect the trigeminal nerve or its branches alone. Symptoms of trigeminal neuropathy depend on the location and etiology of the lesion and may include loss of sensation in the distribution of one or more trigeminal nerve branches, neuropathic pain, or weakness of the muscles of mastication.[14]

Nerve testing

- Facial sensation can be tested by asking the patient to close his or her eyes and report where a stimulus is felt. Light touch with a cotton wool stick, pinprick with the end of a sterile needle, and warm and cold stimuli can be tested on each side of the face.[4] Contraction of the masseter and temporal muscles can be examined by visual inspection, and palpation of the masseter muscles can be examined when the patient is chewing.
- The jaw jerk can be tested as follows: with the patient's mouth slightly open, the mandible is tapped just below the lips in a downward direction. The masseter will move the mandible upward. Normally this reflex is weak, but it may be pronounced with upper motor neuron lesions.[4]
- The strength of the pterygoid muscles may be tested by asking the patient to open the jaw against resistance.[4]
- The corneal reflex can be tested with cotton wool (afferent-trigeminal, efferent-facial) and elicits an ipsilateral and contralateral blink response in normal individuals.[4]
- Electrodiagnostic testing: the afferent component of the trigeminal nerve (V1) may be evaluated via the blink reflex. Needle electromyography of trigeminal nerve-innervated muscles, such as masseter and temporalis, tests for the motor efferent component of the trigeminal nerve (V3). Less common tests of the trigeminal nerve include masseter inhibitory reflex and jaw jerk (the latter is similar to the aforementioned physical exam).[8] [15] [16][17]

Facial (VII)

Anatomy

- The facial nerve is composed of both motor and sensory roots (nervus intermedius) and has a long intracranial course with 3 bends and multiple branches. The motor root has neuronal cell bodies in the facial nucleus of the lateral caudal pons. Fibers from the nucleus course posteriorly and form a sharp loop around the sixth nerve nucleus, forming the facial colliculus. The seventh cranial nerve then exits

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the brainstem at the pontomedullary junction, traverses the cerebellopontine cistern, and enters the facial canal through the meatus of the internal auditory canal. The nervus intermedius carries general somatic afferent and special visceral efferent fibers, and is separate from the motor root only between the brainstem and the facial canal. The geniculate ganglion, containing the cell bodies of general somatic afferent and special visceral efferent neurons, is located in the temporal bone within the facial canal.

- The first branch of the seventh cranial nerve is the greater superficial petrosal nerve, which travels to the sphenopalatine and pterygopalatine ganglion, and carries parasympathetic fibers to innervate the lacrimal gland of the eye. The second branch innervates the stapedius muscle. The chorda tympani (third branch) carries taste sensation from the anterior two-thirds of the tongue, as well as parasympathetic innervation to the sublingual and submandibular glands (through the submandibular ganglion). The facial nerve exits the cranium through the stylomastoid foramen and enters the parotid gland, where it splits into 5 terminal branches (temporal, zygomatic, buccal, mandibular, and cervical), which innervate the muscles of facial expression, and digastric and stylohyoid muscles.

Function and disorders

- Facial nerve mononeuropathy is the most common cranial nerve mononeuropathy. It can affect people of all ages. There are many etiologies, and the most important initial step is to rule out central causes of facial weakness, including ischemic stroke and pontine neoplasms.[4] The most common peripheral facial palsy is Bell palsy.[18]

Nerve testing

- Muscles of facial expression can be tested to determine facial nerve function. Patients are asked to close their eyes tightly and resist opening, raise their eyebrows against resistance, show their teeth, and purse their lips. With a unilateral upper motor neuron lesion, such as a stroke, only the lower half of the face on the contralateral side is affected, due to bilateral innervation of the upper facial muscles.[4] With a lower motor neuron lesion, such as a Bell palsy, there is ipsilateral upper and lower face weakness.
- Electrodiagnostic testing: a combination of facial nerve motor conduction studies, blink reflex testing, and needle electromyography of facial muscles in at least 4 of the 5 terminal branches (temporal, zygomatic, buccal, and marginal mandibular) may be used to determine the extent and severity of facial nerve dysfunction.[15] [16] [17]
- Neuromuscular ultrasonography: the facial nerve can be visualized with high-frequency ultrasonography underneath the ear lobe, and as it enters the parotid gland. This is technically challenging (the facial nerve can be isoechoic [the same echotexture] as the parotid gland), but can be used to assess for compression, focal nerve changes, and nerve continuity.[19]

Vestibulocochlear (VIII)

Anatomy

Cell bodies of the vestibular division reside in the vestibular (Scarpa) ganglion in the internal acoustic meatus. Their dendrites project to the hair cells of the vestibular sensory organs (hair cells in the ampullae of the 3 semicircular canals, and hair cells in the maculae of the utricle and saccule) and axons project to the lateral, medial, superior, and inferior vestibular nuclei in the caudal pons. The cochlear division of the eighth cranial nerve has cell bodies in the spiral (auditory) ganglion with dendrites projecting to the hair cells of the auditory sensory organ (the organ of Corti within the cochlea). Axons of the cochlear division exit the internal

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acoustic meatus and course with the vestibular portion to enter the brainstem at the junction of the pons and medulla (cerebellopontine angle), and synapse in the ventral and dorsal cochlear nuclei of the rostral medulla.

Function and disorders

The vestibulocochlear nerve is a purely special sensory afferent nerve consisting of vestibular and cochlear divisions. Their axons run together through the internal acoustic meatus (which also transmits the facial nerve) and the brainstem. Symptoms of dysfunction include hearing loss, tinnitus, and vertigo.

Nerve testing

- Simple bedside hearing tests such as whispering a word or number in one ear with the other covered and having the patient repeat the word can be used to assess the degree of hearing impairment.[4]
- Rinne test: a tuning fork is placed on the mastoid bone (bone conduction) until the sound can no longer be heard. The tuning fork is then placed next to the external ear (air conduction). Usually air conduction is better than bone conduction, so the sound can still be heard; this is a positive Rinne test. If bone conduction is better than air conduction, this is a negative Rinne test and indicates conductive hearing loss in that ear.[4]
- Weber test: the tuning fork is placed on the forehead. The patient is asked in which ear the sound is louder. If the patient hears the sound equally in each ear or cannot localize, this is normal and is termed a midline Weber. The Weber lateralizes toward a conductive hearing loss and away from a sensorineural hearing loss. For example, if the patient hears the sound louder in the right ear, then this indicates either a right conductive or a left sensorineural hearing loss.[4]
- Electrodiagnostic testing: brainstem auditory evoked potentials (BAEPs) may be performed to identify and localize auditory pathway lesions. This potential is recorded from surface electrodes on the patient's head, while sound is repeatedly played over a headphone or earpiece in either ear.[8] Use of BAEPs has declined due to widespread availability of neuroimaging.

Glossopharyngeal (IX)

Anatomy

The glossopharyngeal nerve exits the rostral medulla at the pontomedullary junction, crosses the cerebellopontine cistern, and exits the cranial cavity through the jugular foramen. It contains general somatic afferent, general visceral efferent, special visceral afferent, and parasympathetic fibers that innervate the tongue and pharynx.[20] Visceral and taste fibers within the nerve end in the nucleus solitarius of the medulla, which also receives afferent fibers from the carotid body and carotid sinus. Preganglionic parasympathetic fibers travel through the tympanic nerve to the lesser petrosal nerve and synapse in the otic ganglion before supplying the parotid gland.

Function and disorders

It is predominantly a sensory nerve but also contains some motor and parasympathetic fibers. Isolated glossopharyngeal neuropathy is rare, as lesions often involve other cranial nerves in close proximity (VIII, X, XI, and XII).[20] Additionally, isolated palsy of the glossopharyngeal nerve can often be asymptomatic, due to redundant innervation of target structures by other cranial nerves. The nerve innervates the tongue and pharynx, including pain, temperature, and tactile sensation from the posterior third of the tongue, the tonsils, medial tympanic membrane, and Eustachian tube. It also innervates the stylopharyngeus muscle, involved in

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swallowing, mediates taste from the posterior third of the tongue, and sends parasympathetic innervation to the parotid gland.[21] [22]

Nerve testing

The gag reflex is absent if a nerve palsy is present, as the afferent impulse is carried by the glossopharyngeal nerve.[4]

Vagus (X)

Anatomy

The vagus nerve exits the brainstem just below the glossopharyngeal nerve, at the pontomedullary junction, traverses the cerebellopontine angle, and exits the cranium through the jugular foramen. The first main branch of the vagus nerve is the pharyngeal branch, which runs in the carotid sheath between the internal and external carotid arteries. It innervates the levator veli palatini, salpingopharyngeus, and palatopharyngeus muscles, and the uvula.[23] The superior laryngeal nerve descends lateral to the pharynx; its external branch innervates the cricothyroid muscle. The recurrent laryngeal nerve is the third motor branch of the vagus and supplies all intrinsic muscles of the larynx except the cricothyroid. The right recurrent laryngeal nerve loops around the right subclavian artery, while the left loops under the aortic arch before ascending in the tracheoesophageal groove to the larynx.[24]

Function and disorders

The vagus nerve contains both visceral efferent and afferent fibers and has 3 main motor branches.[21] It innervates all striated muscles of the larynx and pharynx, except the stylopharyngeus muscle (innervated by IX) and the tensor veli palatini muscle (mandibular branch of V). Sensory input from the larynx, pharynx, external auditory canal, lateral tympanic membrane, and posterior fossa meningeal layers are mediated by the vagus.[25] Visceral afferent information is also conveyed by the vagus nerve from the thoracic and abdominal viscera, and it delivers parasympathetic fibers to these regions as well, in addition to the larynx and pharynx.[18]

Nerve testing

- Tenth nerve palsy can result in hoarseness, dysphagia, and dyspnea, as well as palatal droop and deviation of the uvula to the contralateral side.[4] [18] Lesions distal to pharyngeal branches, or a lesion of the recurrent laryngeal nerve itself, present with isolated hoarseness. The gag reflex is absent, as the efferent limb is formed by the vagus nerve.[18]
- Electrodiagnostic testing: electromyographers experienced in laryngeal needle placement can perform laryngeal electromyography to assess for laryngeal nerve disorder.[17] [26]
- Neuromuscular ultrasonography: the vagus nerve can be visualized with high-frequency ultrasonography in the carotid sheath in the neck at the level of the thyroid, typically in between the carotid artery and internal jugular vein. Sonographic assessment of the nerve at this site can be used to see focal nerve changes, assessing for a demyelinating polyradiculopathy.

Spinal accessory (XI)

Anatomy

The spinal accessory nerve originates in the rostral spinal cord at C1 to C5 levels through a series of rootlets that emerge between the dorsal and ventral roots. It ascends through the foramen magnum and exits the

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skull through the jugular foramen. The fibers of the spinal accessory nerve emerge through the posterior border of the sternocleidomastoid (SCM) muscle and supply both the SCM and the trapezius muscles. As it crosses the posterior triangle of the neck it is closely related to the superficial cervical lymph nodes.[27]

Historically, the spinal accessory nerve and the "cranial root of the accessory nerve" were identified as constituents of a single "accessory nerve." The cranial root originates from the nucleus ambiguous and exits from the lateral aspect of the medulla, briefly joining the spinal accessory nerve before it separates to join the vagus nerve, and innervating the muscles of the soft palate, larynx, and pharynx. Because of its functional similarity, the cranial root is commonly grouped as part of the vagus nerve.[18] [28]

Function and disorders

The spinal accessory nerve is purely a motor nerve and supplies the SCM and trapezius muscles.[4] It is not commonly injured, but due to its long, superficial extracranial course, it is susceptible to iatrogenic injury.[28] Injury to this nerve can result in lateral scapular winging and unilateral inability to shrug the shoulder.

Nerve testing

- The spinal accessory nerve can be assessed by testing the strength of trapezius and SCM muscles. Trapezius weakness results in a drooping shoulder at rest and mild lateral scapular winging with attempted shoulder elevation and arm abduction >90°. When the patient shrugs his or her shoulders against resistance, unilateral weakness may be detected.[4] SCM weakness results in difficulty when turning the head in the opposite direction to the injury. To test, the patient is asked to turn his or her head to the side against resistance.[4] Proximal lesions of the nerve produce weakness of both the SCM and trapezius muscles.
- Electrodiagnostic testing: motor nerve conduction studies of the spinal accessory nerve as well as needle electromyography of the trapezius and/or SCM may be performed to assess for spinal accessory neuropathy.[17]
- Neuromuscular ultrasonography: the spinal accessory nerve can be visualized with high-frequency ultrasonography in the posterior triangle of the neck. This is a technically challenging, but can be used to assess for compression, focal nerve changes, and nerve continuity. Muscle ultrasonography of the SCM and/or three portions of the trapezius muscle (upper, middle, and lower) in the setting of a spinal accessory neuropathy can reveal atrophy, muscular changes, and lack of movement with dynamic assessment.[19] [29]

Hypoglossal (XII)

Anatomy

The hypoglossal nucleus is located in the dorsal aspect of the caudal medulla, just below the floor of the fourth ventricle. General somatic efferent fibers from the nuclei course ventrally to exit the brainstem as two bundles of rootlets at the ventrolateral sulcus of the medial medulla. These rootlets exit the cranium through the hypoglossal canal just rostral to the foramen magnum and unite on the extracranial side. The hypoglossal nerve descends lateral to the internal carotid artery and vagus nerve, and then courses anteriorly to supply the ipsilateral intrinsic and extrinsic (genioglossus, styloglossus, and hyoglossus) muscles of the tongue. Additionally, efferent motor fibers from C1 course along the hypoglossal nerve for a short distance before leaving to innervate the geniohyoid and thyrohyoid muscles, and form the superior root of the ansa cervicalis. Meningeal branches from C1 and C2 innervating the dura mater of the posterior fossa are also carried by the hypoglossal nerve.[30] Finally, the hypoglossal nerve receives sympathetic fibers from the superior

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cervical ganglion and communicates with the lingual branch of the mandibular nerve, which mediates tactile sensation from the anterior two-thirds of the tongue.[18] [31]

Function and disorders

The 12th nerve is purely motor in function. It moves and alters the shape of the tongue by providing ipsilateral motor innervation to the intrinsic and extrinsic tongue muscles.[4] Lesions of the medulla (nuclear lesions) can cause 12th nerve dysfunction but are usually associated with other neurologic symptoms and cranial nerve deficits.

Nerve testing

- A 12th nerve mononeuropathy can be due to nuclear (medullary) or infranuclear lesions. Close exam of the tongue at rest and in motion can help establish this diagnosis. Symptoms of a 12th nerve palsy typically include unilateral or bilateral tongue weakness with deviation toward the affected side on tongue protrusion, tongue atrophy (with scalloping or accentuation of the midline groove), fasciculation of the tongue at rest, tongue flaccidity, or the inability to rapidly move the tongue side to side or vertically.[4]
- Electrodiagnostic testing: needle electromyography of the intrinsic tongue muscles, such as the genioglossus muscle, may be performed to assess for hypoglossal neuropathy or motor neurone disease.[17] [32]
- Neuromuscular ultrasonography: muscle ultrasonography of the intrinsic tongue muscles is a more sensitive tool than needle electromyography to reveal tongue fasciculations in motor neurone disease. Focal changes in the echotexture of the hypoglossal-innervated muscles can be visualized; however, the hypoglossal nerve is not readily seen.[33]

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Etiology

There are 12 paired cranial nerves, named and numbered according to the rostral-caudal order of attachment to the brain. They serve a variety of functions, and predominantly provide the motor and sensory innervation to the head. The effects of a mononeuropathy depend on where in its pathway the nerve is affected and the etiology.

Olfactory (I)

Most chronic anosmia or hyposmia is due to etiologies that do not damage the olfactory nerve itself. These include upper respiratory tract infection (including COVID-19), head trauma, nasal/paranasal sinus disease, and toxins such as hydrogen sulfide.[34] [35] Factors such as age, sex, and smoking behavior can influence olfaction.[5]

Olfactory disturbances secondary to olfactory nerve involvement include the following.

- Head trauma: the prevalence of precedent head trauma in olfactory dysfunction is 4% to 15% and up to 20% in those who attend a specialized chemosensory center.[35] Occipital and side impacts are most likely to result in olfactory deficits; frontal impacts, the least.[36] Olfactory dysfunction is related to coup-contrecoup forces that cause a shearing of the olfactory filaments as they pass through the cribriform plate. Less than half of patients show any subsequent recovery in their olfaction.[36] [37] In those that do have some improvement, the process typically takes many months.
- Neurodegenerative disease: olfactory dysfunction is a cardinal feature of several neurodegenerative diseases, such as Alzheimer disease and Parkinson disease.[38] Deficits are present in 85% to 90% of people with early-stage disease and are associated with decreased activation of central olfactory elements.[39] The magnitude of dysfunction is not associated with disease stage, severity of motor symptoms, or neurocognitive function. Multiple sclerosis (MS) can result in smell dysfunction proportional to plaque burden.[40] In these cases, olfactory dysfunction waxes and wanes during periods of remission and exacerbation.
- Congenital: patients with apparent congenital anosmia usually lack or have hypoplasia of the olfactory bulbs.[2] Kallmann syndrome is a genetic disorder that results in dysplasia of the olfactory bulbs and hypothalamopituitary axis abnormalities.[41]
- Intracranial mass lesion: olfactory groove meningiomas and mass lesions of the frontal lobe can result in anosmia ipsilateral to the lesion. Foster Kennedy syndrome is ipsilateral anosmia associated with optic atrophy with contralateral papilledema.[42]
- Hereditary: Refsum disease (hereditary motor and sensory neuropathy type IV) is a rare cause of anosmia.

Optic (II)

Given the critical importance of sight, the optic nerve is perhaps the most important of the cranial nerves. Disorders affecting its function demand rapid and thorough evaluation.[6]

- Ischemic optic neuropathy is the most common optic neuropathy in adults >50 years old.[43] Nonarteritic anterior ischemic neuropathy is the most common subtype. Risk factors for microvascular disease are common in this population of patients.[44] About 15% of patients with ischemic optic neuropathy will develop involvement of the contralateral eye within 5 years.[6] [45] Arteritis accounts for 6% to 14% of cases of ischemic optic neuropathy, primarily in patients >65 years old.[46] Arteritic

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optic neuropathy, usually giant cell arteritis, can result in severe loss of vision. Varicella zoster vasculopathy has been identified as a potential mimic of giant cell arteritis in biopsy-negative cases.[47]

- MS is one of the major causes of optic neuritis, occurring in 50% of patients at some point in their illness.[48] Population-based data suggest optic neuritis incidence of approximately 4 per 100,000 person-years; women are affected more than men.[49] [50] Those affected are usually between the ages of 18 and 40 years. Visual acuity largely recovers in 2 to 12 weeks, and recovery is hastened (although not improved) by treatment with intravenous methylprednisolone.[51]
- Other autoimmune/inflammatory conditions: optic neuropathy is a complication in 5% to 15% of patients with sarcoidosis and can be the initial presentation.[52] Optic neuritis is a rare manifestation of systemic autoimmune disorders, including systemic lupus erythematosus (SLE), Sjogren syndrome, granulomatosis with polyangiitis, and Behcet disease.[50] Neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein-associated disorder (MOGAD) are demyelinating conditions affecting the optic nerves and central nervous system that are pathophysiologically distinct from MS and associated with serologic markers.[53] NMOSD and MOGAD are both commonly associated with optic neuritis and longitudinally extensive myelitis. A relapsing course is more common with NMOSD while monophasic course is seen in half of the patients among MOGAD. While both can have aggressive and severe attacks, patients with MOGAD can have more favorable recovery compared with patients with NMOSD.[54]
- Viral infections: can cause isolated infection of the eye and produce neuroretinitis, which results in a triad of visual loss, swollen optic disk, and a macular star.[6] Visual loss can be mild or severe, but vision recovers completely in 90% of patients. Postviral optic neuritis has been associated with measles, mumps, chickenpox, and influenza, and typically follows the clinical infection by 1 to 3 weeks. It has also been reported as a postimmunization phenomenon.
- Optic canal trauma: injury may be caused by a tear, avulsion, contusion, or hemorrhage within the optic canal. Trauma is frequently to the outer brow or adjacent temporal bone.[55] Spontaneous recovery is well documented, occurring in about 50% of patients, and likely reflects a conduction block rather than a transection.
- Compressive lesions are usually neoplastic. Optic nerve sheath meningiomas can originate anywhere along the retrobulbar optic nerve and predominantly affect women of middle age.[6] Optic nerve gliomas occur mainly in the first and second decades of life, and about one third of patients have neurofibromatosis.[56] Sellar and parasellar masses (craniopharyngioma, meningioma, and pituitary tumors) can compress the optic nerve and chiasm, resulting in slowly progressive visual loss in the bitemporal visual fields.[6]
- Idiopathic intracranial hypertension results in swelling of the optic disk in most patients, but not all experience symptoms. It can affect all ages but typically affects young women, particularly those with obesity.
- Hereditary optic neuropathies, such as dominant optic atrophy (DOA) and Leber hereditary optic neuropathy (LHON), are causes of progressive visual loss.[57] They are both ultimately bilateral but may present asymmetrically. LHON predominantly affects young men and is inherited from the maternal side through mitochondrial DNA mutations.[57] [58]
- IgG4 disease causing pachymeningitis is a rare cause of optic neuropathy.[59] [60] IgG4 disease is an inflammatory condition which can affect a variety of systems/organs (e.g., pancreato-biliary tract, retroperitoneum/aorta, and salivary glands), but it can also produce infiltrates at the base of the skull, which affect the cranial nerves. The imaging appearances can mimic other causes of basal skull infiltration, such as a tumor or granulomatous disease. Diagnosis is by biopsy and IgG4 disease is usually highly responsive to corticosteroid and immune treatment.[59] [60]

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- Drugs such as ethambutol, infliximab, sildenafil, and amiodarone have all been implicated in optic neuropathy.[61]
- Nutritional deficits have a presumed role in endemic outbreaks of optic neuropathy in situations of deprivation. Vitamins B1 (thiamine), B2 (riboflavin), B9 (folate), and B12 (cobalamin) have been implicated.[62] Chronic excessive alcohol can also result in vitamin deficiencies.

Oculomotor (III), trochlear (IV), and abducens (VI)

Dysfunction of the third cranial nerve can result from a lesion anywhere along its path between the midbrain nucleus and innervation of the extraocular muscles in the orbit.[63]

Isolated third nerve palsies can be divided into acquired, traumatic, and congenital.

Acquired third nerve palsy

Can be further subdivided according to pupillary involvement and degree of extraocular muscle dysfunction:[64]

- Normal pupillary function with complete ophthalmoplegia (occurs when the lesion is confined to the inner somatomotor fibers of the nerve innervating the extraocular muscles, and does not disrupt the outer pupillomotor fibers)
- Normal pupillary function with incomplete ophthalmoplegia (may be due to intracranial aneurysm or vascular malformation, disrupting the outer pupillomotor fibers of the oculomotor nerve)
- Pupillary dysfunction with partial or complete ophthalmoplegia (most often due to compressive lesions or meningeal infiltration).

Drugs may cause an acquired third nerve palsy with normal pupillary sphincter and complete ophthalmoplegia. These may follow use of sildenafil and cocaine.[65] [66]

Migraines can lead to temporary third nerve mononeuropathy with headache, photophobia, and nausea, but consciousness is not impaired.[67]

Traumatic third nerve palsy

Raises suspicion for an underlying cerebral lesion in a patient with minor head trauma, and should prompt immediate further work-up.

Congenital third nerve palsy

Rare, and are usually diagnosed in the first 3 months of life.[9] They may occur in isolation or be associated with other neurologic or systemic congenital abnormalities. Congenital fourth and sixth nerve palsies are extremely rare.[9] [68]

Dysfunction of third, fourth, or sixth cranial nerve

Progressive symptoms of third, fourth, or sixth nerve palsy may be due to a compressive intracranial lesion. A third nerve palsy can indicate serious underlying pathology such as subarachnoid hemorrhage or uncal herniation.[69] Structural anomalies such as pituitary or skull base base tumors, cavernous sinus thrombosis, or a vascular malformation (such as a cerebral aneurysm or a cavernous-carotid fistula) may compress cranial nerves III, IV, or VI.

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Meningitis (viral, bacterial, fungal, tuberculous, sarcoid, or carcinomatous) may result in meningismus and cause third, fourth, or sixth nerve palsy. Third nerve palsy typically presents with pupillary dysfunction and partial or complete extraocular muscle palsy. Cranial nerve palsies are seen in 9% of cases of community-acquired bacterial meningitis, and are predictive of a less favorable outcome when present.[70] Infrequently, sixth nerve palsies can occur after an LP.[71] [72]

IgG4 disease causing pachymeningitis is a rare cause of abducens neuropathy.[59] [60] IgG4 disease is an inflammatory condition which can affect a variety of systems/organs (e.g., pancreato-biliary tract, retroperitoneum/aorta, and salivary glands), but it can also produce infiltrates at the base of the skull, which affects cranial nerves. The cranial nerves II to VI are commonly affected.[60] [73] The imaging appearances can mimic other causes of basal skull infiltration, such as a tumor or granulomatous disease. Diagnosis is by biopsy and IgG4 disease is usually highly responsive to corticosteroid and immune treatment.[59] [60]

Risk factors for ischemia and microvasculopathy include diabetes mellitus, hypertension, and tobacco use. A third nerve palsy with normal pupillary sphincter and complete ophthalmoplegia is most commonly the result of ischemia (50% to 60%), especially when associated with diabetes mellitus.[9] [63] Arteritic involvement (giant cell arteritis) should be considered in older adults.[74] Sixth nerve palsies as a result of ischemia typically improve in 1-3 months, and fourth nerve palsies often resolve spontaneously within 6 months.[9] [75]

Idiopathic intracranial hypertension can affect all ages but typically affects young women, particularly those with obesity, and compresses cranial nerves as they leave the brainstem.[76] The sixth nerve is most commonly affected.

The lengthy course of the fourth cranial nerve makes it particularly susceptible to traumatic injury, and this is the most common known cause of isolated fourth nerve palsy. Trauma would usually be severe enough to cause loss of consciousness.[77] [78] The sixth nerve has the longest subarachnoid course, and is also susceptible to traumatic damage.

Trigeminal (V)

Lesions can affect the nuclei of the trigeminal nerve within the brainstem (intra-axial) or the trigeminal nerve itself (extra-axial). Trigeminal mononeuropathy is more often the result of extra-axial lesions. Intra-axial lesions often result in additional neurologic and cranial nerve deficits due to the close anatomic proximity of other critical structures.

- Meningitis (bacterial, fungal, tuberculous, sarcoid, or carcinomatous) may result in meningismus and/or fever with trigeminal nerve palsy.
- Posterior inferior cerebellar artery stroke can cause lateral medullary (Wallenberg) syndrome. This is characterized by sensory deficits on the opposite side of the body and affects the ipsilateral cranial nerves, facial sensation, and motor supply. The effects on the trigeminal nucleus result in loss of ipsilateral facial sensation and the corneal reflex. It does not cause an isolated fifth nerve neuropathy.
- Trigeminal neuralgia may be caused by any lesion that compresses the trigeminal nerve as it traverses the cerebellopontine and prepontine cisterns.[79] Compression of the nerve by an aberrant vascular structure is thought to be responsible for most idiopathic cases. These include aberrant vessels (in particular the superior cerebellar artery) or an unruptured intracranial aneurysm.[80] Diagnosis is usually clinical, but onset in a patient ages <55 years should be investigated with cerebral imaging.[81] Incidence of trigeminal neuralgia peaks at age >60 years.[82] [83] [84]
- Pontine hemorrhage due to a vascular malformation may cause sudden and enduring trigeminal sensory impairment in the absence of any other neurologic findings. A second form, termed

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symptomatic, is caused by lesions other than vascular compression, typically meningioma, schwannoma, epidermoid and arachnoid cysts, or malignant neoplasm, that can be demonstrated on brain MRI.[85] These patients are more likely to have concomitant neurologic deficits.

- MS may cause a demyelinating lesion in the pons. Trigeminal neuralgia is rarely the presenting symptom, as it tends to occur in advanced disease.
- High cervical spinal cord lesions can affect the spinal trigeminal tract as it extends caudally to the level of C2.
- Metastasis from extracranial tumors, such as nasopharyngeal carcinoma and neck malignancies, may spread along the course of the trigeminal nerve to the Meckel cave. Numb chin syndrome may occur due to metastasis to the mandible involving the mental nerve (a branch of the inferior alveolar nerve).
- Local infections, such as a skull-base osteomyelitis, can cause trigeminal neuropathy. A dental abscess near the third molar tooth can result in a neuropathy of the mandibular division.
- Herpes zoster can cause severe neuralgia in the trigeminal distribution, most commonly in the ophthalmic division. The condition is self-limited and remits in 3-4 days, but in a few patients (about 10%) pain can persist for several months and is known as postherpetic neuralgia.[86]
- Autoimmune trigeminal neuropathy is rare but causes include Sjogren syndrome, systemic lupus erythematosus (SLE), and systemic sclerosis.[87]
- IgG4 disease causing pachymeningitis is a rare cause of trigeminal neuropathy.[59] [60] IgG4 disease is an inflammatory condition which can affect a variety of systems/organs (e.g., pancreato-biliary tract, retroperitoneum/aorta, and salivary glands), but it can also produce infiltrates at the base of the skull, which affects cranial nerves. The cranial nerves II to VI are commonly affected.[60] [73] The imaging appearances can mimic other causes of basal skull infiltration, such as a tumor or granulomatous disease. Diagnosis is by biopsy, and IgG4 disease is usually highly responsive to corticosteroid and immune treatment.[59] [60]
- Orbital, midface, mandibular, or skull-base fractures can result in trigeminal neuropathy.
- Congenital causes include aplasia or hypoplasia of the trigeminal nerve and Chiari type I and II malformations.
- Iatrogenic injury may occur to the inferior alveolar nerve (V3 division) during oral surgery or cosmetic liquid nitrogen procedures.[88]
- A rare cause of trigeminal neuropathy is Tolosa-Hunt syndrome. It is a nonspecific inflammation of the superior orbital fissure, often extending into the cavernous sinus with sparing of the pupillary function.[89] This often includes painful ophthalmoplegia (due to involvement of nerves III, IV, and VI). Symptoms last days to weeks with spontaneous remission and recurrent attacks but no systemic involvement.

Facial (VII)

This is the most frequently diagnosed cranial neuropathy, with myriad potential etiologies.[90]

It affects patients of both sex and at any age.

- Bell palsy is the most common etiology of facial paralysis, accounting for up to 70% of all facial neuropathies.[91] It is a diagnosis of exclusion and is defined as a facial palsy with no known cause or associated neurology. It is thought to be due to a viral demyelinating neuritis, likely secondary to herpes simplex virus reactivation in the geniculate ganglion.[92] [93]
- Ramsay Hunt syndrome accounts for about 3% to 18% of cases of peripheral facial paralysis.[94] [95] It is a rare neurologic condition characterized by reactivation of the varicella zoster virus involving the facial nerve, and less commonly other cranial nerves (e.g., V, IX, and X).[96] Patients often present

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with a triad of symptoms: sudden-onset (<72 hours) ipsilateral peripheral facial palsy, severe ear/facial pain, and vesicular ear rash.[96] However, many patients do not present with all three classic features concomitantly; vesicles can precede, coexist, or follow facial palsy. Other cranial nerves, particularly VIII (with hearing loss and tinnitus), IX, and X, may also be involved, differentiating this etiology from Bell palsy.

- Central facial palsy is most commonly the result of a lesion in the contralateral motor strip (precentral gyrus) or corticobulbar tract, usually from ischemic stroke. A nuclear facial palsy may also result from a lesion involving the facial nucleus such as ischemia or a neoplasm. Involvement of adjacent structures often results in additional neurologic findings, such as ipsilateral sixth cranial nerve (abducens) palsy or contralateral limb weakness.
- Basal skull fracture is another common cause of an isolated facial nerve palsy. It can result in injury proximal to the origin of chorda tympani. Temporal bone fracture can also result in facial nerve paralysis.
- Meningitis (bacterial, fungal, tuberculous, sarcoid, or carcinomatous) may result in meningismus and/or fever with a resulting facial nerve palsy. Other cranial nerves may also be affected.
- Cerebellopontine angle tumors/cysts can compress the facial nerve. The most common tumors responsible are benign schwannomas. Other, less common, masses include arachnoid cysts, meningiomas, and epidermoid cysts.
- Iatrogenic injury to one or more of the branches of the facial nerve is a risk of parotid gland and otologic surgery, due to the nerve's close proximity.
- Local infections such as otitis media or mastoid infection can affect the facial nerve. Neuropathy usually responds to treatment of the underlying infection.[97]
- Tumors of the parotid gland may also cause facial weakness through involvement of some (but often not all) terminal branches of the facial nerve.
- Facial neuropathy may be associated with human immunodeficiency virus (HIV). It may develop as an isolated finding or in combination with peripheral neuropathy.
- Lyme disease is a frequent cause of bilateral facial neuropathy and accounts for 50% of patients with neurologic involvement.[98]
- IgG4 disease causing pachymeningitis is a rare cause of facial neuropathy.[59] [60] IgG4 disease is an inflammatory condition which can affect a variety of systems/organs (e.g., pancreato-biliary tract, retroperitoneum/aorta, and salivary glands), but it can also produce infiltrates at the base of the skull, which affects cranial nerves. The cranial nerves V, VI, and VII seem most commonly affected, with subacute or chronic symptoms.[60] The imaging appearances can mimic other causes of basal skull infiltration, such as a tumor or granulomatous disease. Diagnosis is by biopsy; and IgG4 disease is usually highly responsive to corticosteroid and immune treatment.[59] [60]
- Other causes of facial nerve palsy include Guillain-Barré syndrome and its variants (often bilateral), diabetes mellitus, pregnancy, amyloidosis, and neurosarcoidosis.[99] Metastasis to the temporal bone can compress the nerve in the facial canal.

Vestibulocochlear (VIII)

Vestibulocochlear nerve dysfunction is a frequent cause of hearing loss, tinnitus, or vertigo resulting from damage to either the cochlear or the vestibular portion of the eighth cranial nerve between the inner ear and its entry into the brainstem at the pontomedullary junction.

Sudden sensorineural hearing loss is defined as loss of >30 decibels in 3 sequential frequencies within 72 hours.[100] It is due to dysfunction of the cochlea or the vestibulocochlear nerve itself, but the underlying etiology is unknown.

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Known causes of eighth nerve dysfunction and/or palsy include the following.

- Vestibular neuritis (also known as vestibular neuronitis, labyrinthitis, and acute peripheral vestibulopathy) that is usually secondary to acute viral or postviral inflammation of the vestibular division of the eighth cranial nerve.[101] It is a self-limited condition.
- Neural presbycusis, an age-related hearing loss caused by atrophy of nerve cells in the cochlea. It is characterized by high-frequency loss and profound reduction in speech discrimination.[102]
- A tumor/cyst in the cerebellopontine angle can compress the eighth nerve.[18] The most common mass is a schwannoma arising from the vestibular division of the nerve. A history of neurofibromatosis may support this diagnosis. Other masses that can produce similar symptoms include meningiomas, arachnoid cysts, and epidermoid cysts.
- IgG4 disease causes pachymeningitis and is a rare cause of vestibulocochlear neuropathy.[59] [60] IgG4 disease is an inflammatory condition which can affect a variety of systems/organs (e.g., pancreato-biliary tract, retroperitoneum/aorta, and salivary glands), but it can also produce infiltrates at the base of the skull, which affects cranial nerves. The imaging appearances can mimic other causes of basal skull infiltration, such as a tumor or granulomatous disease. Diagnosis is by biopsy; IgG4 disease is usually highly responsive to corticosteroid and immune treatment.[59] [60]
- Ototoxic drugs include aminoglycosides, platinum-based antineoplastic agents, salicylates, quinine, and loop diuretics.[102] Hearing loss from drug toxicity is usually irreversible.[103]

Glossopharyngeal (IX) and vagus (X)

Factors that help differentiate between specific etiologies for cranial nerve IX and X neuropathies include the duration since onset and a history of recent head or neck surgery.

- The single most common tenth nerve lesion is iatrogenic injury to the right or left recurrent laryngeal nerve during neck or thoracic surgery. It accounts for about one third of all vocal cord paralysis.[20]
- Tumors/cysts, including cerebellopontine angle masses, schwannomas of the eighth or ninth nerve, meningiomas, arachnoid cysts, and epidermoid cysts, can cause compression, but other cranial nerves are often affected. Compression may also be caused by masses of the jugular foramen and parapharyngeal space, including glomus jugulare tumors and carotid body tumors (both paragangliomas). Apical lung tumors or high thoracic tumors may impinge on the recurrent laryngeal nerve (particularly the left side), resulting in hoarseness.
- Meningitis (bacterial, fungal, tuberculous, sarcoid, or carcinomatous) may result in meningismus and/or fever. Other cranial nerves may also be affected.
- Local infections, including the skull base and parapharyngeal space, can affect the ninth and tenth cranial nerves.
- Skull-base fracture can affect these nerves, although ninth or tenth cranial neuropathy is unlikely to be an isolated finding.
- Eagle syndrome is an irritation of the ninth cranial nerve by an elongated styloid process. It may result in glossopharyngeal neuralgia, which is characterized by paroxysmal episodes of unilateral pain in the base of the tongue and deep neck, and is usually elicited by chewing or swallowing.[104]
- Cardiovocal syndrome is hoarseness due to impingement of the left recurrent laryngeal nerve as it passes between the aorta and the pulmonary artery. It can be seen in a range of cardiovascular conditions, including left atrial enlargement due to mitral stenosis.[105]

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Spinal accessory (XI)

The spinal accessory nerve innervates the sternocleidomastoid and trapezius muscles. Injury to this nerve is uncommon.

- Iatrogenic injury is the most common cause of isolated eleventh nerve injury. This usually occurs during surgery in the posterior triangle of the neck during lymph node biopsy or radical neck dissection.[27] Damage may also occur during jugular vein cannulation, carotid endarterectomy, or cosmetic rhytidectomy (face lift).[106] [107]
- Blunt or penetrating trauma may also result in an isolated spinal accessory palsy.
- Tumors/cysts may include include large lesions of the cerebellopontine angle extending downward toward the foramen magnum, rostral intrinsic spinal cord tumors (typically the tenth nerve is also affected), and jugular foramen tumors. Jugular foramen tumors can produce 3 characteristic syndromes involving the spinal accessory nerve:[18] [108]
    - Vernet syndrome (neuropathy of IX, X, and XI)
    - Collet-Sicard syndrome (neuropathy of IX, X, and XI, plus cerebellar disturbance)
    - Villaret syndrome (neuropathy of IX, X, XI, and XII).

Hypoglossal (XII)

Mononeuropathy of the twelfth cranial nerve is rare. Causes can be nuclear (affecting the nucleus of the nerve in the caudal medulla) or infranuclear (lesions of the nerve itself as it travels from the brainstem to its target muscles). Additionally, motor neurone disease or progressive bulbar palsy (a bulbar form of amyotrophic lateral sclerosis) can result in dysfunction. Causes of twelfth nerve dysfunction include the following.[18] [109]

- Nuclear (medullary) lesions, these including ischemic lesions resulting in a brainstem stroke and medullary neoplasms. The progressive bulbar palsy variant of amyotrophic lateral sclerosis and Chiari malformations can also result in a nuclear hypoglossal nerve palsy. Due to the close anatomic proximity of other structures in this region, other neurologic findings are common.
- Multiple types of tumors and masses at the skull base. These include metastatic tumors, meningioma, glomus jugulare tumor, chordoma, osteoma, sarcoma, nerve sheath tumors, epidermoid or dermoid cysts, arachnoid cyst, and carcinoma of the tongue or nasopharynx.
- Meningitis (bacterial, fungal, tuberculous, sarcoid, or carcinomatous) may result in meningismus and/or fever. Other cranial nerves may also be affected.
- Local infections may include skull-base osteomyelitis and neck abscess.
- Skull-base fracture and penetrating injuries to the neck (such as gunshot wounds) can cause isolated hypoglossal injury.
- Iatrogenic injuries can result from irradiation of the neck, from surgical injury during neck dissection or carotid endarterectomy, or during central venous line placement.
- Vascular malformations, such as a dural arteriovenous fistula, or internal carotid artery aneurysm or dissection may present as an isolated twelfth nerve palsy.

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Urgent considerations

(See **Differentials** for more details)

Meningitis

The meninges may become inflamed in response to viral, bacterial, or fungal infection, carcinomatosis, or neurosarcoidosis. The patient will typically be ill, and clinical features may include photophobia, fever, stiff neck, headache, and rash (typically a nonblanching rash of meningococcal septicemia). Cranial nerves III, V, VII, IX, X, and XII may be affected, and a neuropathy may present either in isolation or in combination. An urgent brain computed tomography (CT) is needed to exclude other urgent causes, followed by a lumbar puncture (LP) to obtain a sample of cerebrospinal fluid (CSF) for microscopy and culture.[110] Broad-spectrum antibiotics should be given presumptively if meningitis is suspected, ideally after blood cultures are collected.

Arteritic ischemic optic neuropathy (giant cell arteritis)

Diagnosis should be considered in a patient 50 years or older who presents with new onset temporal headache, visual disturbances, or jaw or tongue claudication.[111] Approximately one third of patients will have symptoms of polymyalgia rheumatica, characterized by pain and stiffness in the head and neck and proximal upper and lower extremities. Constitutional symptoms including fatigue, weight loss, malaise, and fever also are common presenting symptoms.

These patients can develop rapid visual loss due to optic neuropathy that is preventable with timely use of corticosteroids. Screen with erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP). If these are elevated, high-dose corticosteroids should be started and a temporal artery biopsy arranged to confirm the diagnosis.[112] Rarely patients may present with neuropathies of cranial nerves III, IV, or VI.[74] Patients should be evaluated by a specialist, ideally on the same working day if possible, and in all cases within three working days.[112]

Subarachnoid hemorrhage

This may follow rupture of a cerebral aneurysm or bleeding after a head injury. The patient presents with a sudden-onset severe headache or sudden altered consciousness, and there may be vomiting, neck stiffness, or seizures. An isolated dilated pupil may reflect rising intracranial pressure and herniation. A third, fourth, or sixth nerve palsy may be evident, and urgent CT/magnetic resonance imaging scan (MRI) brain is needed. If confirmed, an urgent neurosurgical consult is required.

If brain imaging is negative but the index of clinical suspicion for subarachnoid hemorrhage remains high, then a lumbar puncture looking for evidence of recent bleeding (xanthochromia) should be performed.[113]

Cerebral aneurysm

Patients with acquired, nontraumatic, isolated third nerve palsy with pupillary involvement should be evaluated for the presence of an unruptured intracranial aneurysm that may be compressing the third cranial nerve in the subarachnoid space. Initial evaluation with a cerebral or CT angiogram is recommended.

Uncal herniation

A new third nerve palsy with pupillary involvement can be a sign of impending uncal herniation. These patients demand rapid evaluation with a head CT. If neuroimaging cannot be obtained urgently and suspicion

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for herniation is high, presumptive treatment with hyperventilation and/or mannitol can be temporarily instituted. This may occur with increased intracranial pressure.

Intra-axial lesion

Acute onset of a trigeminal neuropathy, often accompanied by other neurologic signs, may suggest a brainstem lesion such as pontine stroke or hemorrhage, or spinal cord pathology, such as cervical disk disease. Brain or cervical MRI as appropriate is recommended.[81]

Guillain-Barré syndrome and its variants

Acute immune demyelinating polyneuropathy (commonly referred to as Guillain-Barré syndrome) predominantly presents with limb weakness. Cranial motor involvement can also be seen. This may range from facial motor weakness, to oropharyngeal weakness (difficulty swallowing), to ophthalmoparesis. Some variants such as Miller-Fisher syndrome (ophthalmoplegia, ataxia and areflexia) and facial diplegia variant may manifest with predominant cranial motor dysfunction.[114] [115]

Prompt investigation, such as CSF analysis, electrodiagnostic studies, and neuroimaging (MRI of neuraxis and/or peripheral nerve ultrasonography), is recommended.

Skull-base osteomyelitis

Neuropathy of nerve V, IX, X, or XII associated with otalgia, otorrhea, hearing loss, and headaches, with or without fever, may herald a diagnosis of skull-base osteomyelitis. Patients should undergo head CT and MRI to assess for bony destruction and soft-tissue changes.

Herpes zoster ophthalmicus

Herpes zoster in the V1 distribution of the trigeminal nerve can cause keratitis, corneal scarring, and visual loss. Therefore, a prompt ophthalmologic consult is warranted to prevent permanent damage.

Trauma

Head trauma that results in an isolated or multiple cranial nerve neuropathy needs urgent evaluation. Noncontrast thin-section head CT should be performed, with special attention to possible orbital, midface, mandibular, or skull-base fractures. Skull-base fracture may account for deficits in cranial nerves VII, IX, or X.

Ischemic stroke (cerebral infarct)

It is critical to exclude a central cause of a seventh cranial nerve palsy of acute onset. Cortical or pontine strokes can often be recognized based on history and neurologic exam findings, including sparing of the upper face (cortical) and presence of associated neurologic deficits, including contralateral limb weakness or altered mental status.

In the hyperacute setting, these findings should prompt immediate neuroimaging and assessment to determine whether the patient is a candidate for thrombolysis and/or mechanical thrombectomy.

Parapharyngeal space infection

Ninth, tenth, or twelfth nerve palsy in the setting of neck pain and fever may be due to a parapharyngeal space infection. Routine blood tests should be performed to include complete blood count (CBC), CRP, and blood cultures. A neck CT with contrast will confirm the diagnosis.[116]

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Medullary lesion

Lesions of the medulla can rarely result in isolated hypoglossal nerve palsy. They are more commonly associated with additional neurologic findings and cranial nerve deficits. If one is suspected, assessment with prompt brain MRI is warranted.

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Approach

The general approach to any cranial neuropathy is to establish whether it is an isolated finding or if there are other neurologic symptoms or signs. The patient may not be aware of these, and a thorough neurologic exam is needed.

If several cranial nerve defects are identified, the possible diagnosis can be varied, and intracranial imaging is usually required. Clinical history and associated exam findings are crucial in narrowing down the possible causes of a cranial nerve neuropathy and directing further imaging. Urgent considerations should always be excluded first.

Olfactory (I)

Patients with olfactory nerve dysfunction are often unaware of their deficit and infrequently present to a clinician.[2] Those who do present may have anosmia (complete loss of smell), hyposmia (partial lack of smell), dysosmia (normal smells inaccurately detected as unpleasant odors), phantosmia (olfactory hallucinations), or a loss of taste sensation.[4]

Establishing the cause of olfactory loss relies heavily on history.[117] Olfactory dysfunction is often due to causes other than olfactory nerve damage, such as an age-related decline in olfactory function, viral infections or chronic sinus disease, exposure to possible toxins such as pesticides, solvents, heavy metals, or hydrogen sulfide, septal surgery, or radiation. A feeling of unilateral nasal blockage or pressure may suggest an intranasal neoplasm, but this is also rare.

Given the relationship with neurodegenerative diseases such as Alzheimer disease and Parkinson disease, early signs of cognitive or motor dysfunction should be sought.[38]

Patients with congenital abnormalities such as Kallmann syndrome either do not go through puberty or have incomplete puberty if untreated. Male patients with Kallmann may experience decreased libido and erectile dysfunction, while women may have dyspareunia. Both will usually be infertile if left untreated.

There may be evidence of previous head trauma, and a temporal relationship to olfactory dysfunction would support this etiology. Occipital and side impacts are most likely to affect olfactory function.[36] If anosmia is ipsilateral, fundoscopy is indicated to assess for optic atrophy or papilledema, which may indicate an intracranial mass lesion or Foster Kennedy syndrome.

Most patients will have a nonneurologic cause for their olfactory loss and do not require imaging. Clinicians should not necessarily obtain magnetic resonance imaging (MRI) in adult patients with olfactory dysfunction who have no identifiable cause after a thorough history and physical exam (including nasal endoscopy), together with negative findings for preceding viral illness or head trauma.[118]

If imaging is required, MRI scan of the orbits, face, and neck (without and with contrast) is usually appropriate for examining the olfactory nerve and its pathway, although computed tomography (CT) is useful in cases of trauma, paranasal sinus disease, and bony anatomy that impacts olfaction.[119]

Optic (II)

Clinicians should determine whether visual loss is sudden or progressive, monocular or binocular, and whether it is associated with pain. Optic nerve lesions typically produce monocular visual loss. Pain is variable, but when present suggests optic nerve disease such as multiple sclerosis (MS).

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Trauma to the outer brow or temporal bone may cause optic nerve trauma.[55] If a fracture is suspected, orbital CT is advised, with brain imaging if indicated (depending on the presence of any other features such as alteration in consciousness level).[120]

In patients with sudden visual loss and a positive family history, Leber hereditary optic neuropathy (LHON) or dominant optic atrophy (DOA) may be considered. The contralateral eye is usually affected within days to months. In addition, a multiple sclerosis-like illness also sometimes occurs in patients with LHON, especially in women. Diagnosis is confirmed by molecular genetic testing. [NCBI: Leber hereditary optic neuropathy] (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0917796)

Use of certain drugs such as ethambutol, infliximab, sildenafil, and amiodarone may damage the optic nerve, and a trial discontinuation or substitution with an alternative drug is recommended.[61] If there is an epidemic of optic neuropathy (usually in the developing world), nutritional deficiency of B-group vitamins (B1, B2, B9, and/or B12) may be responsible.[62] Formal visual field testing is recommended, and bilateral central scotoma is the most common finding.

Children with disk swelling on fundoscopy are likely to have optic neuritis. A history of preceding viral infection or immunization may be elicited. If disk swelling is absent, further evaluation is recommended with a lumbar puncture (LP), cerebrospinal fluid (CSF) evaluation, and/or brain MRI to look for an intracranial or intraorbital mass lesion or idiopathic intracranial hypertension.

In young adults, optic neuritis is often the first presentation of MS. It affects women more frequently. Most cases are retrobulbar, so most patients have a normal fundus, but one third have papillitis.[62] Loss of color vision and a central scotoma are common findings. There may be associated symptoms of tingling, numbness, or weakness in the limbs. If symptoms are bilateral, are associated with fever, or are atypical for optic neuritis, then a brain MRI is essential to exclude inflammatory or compressive optic neuropathies such as sarcoid tumor, optic nerve meningioma or glioma, or pituitary tumor. MRI may show white matter hyperintensities consistent with MS. Severe or bilateral optic neuritis should raise the possibility of neuromyelitis optica spectrum disorder (NMOSD) or myelin oligodendrocyte glycoprotein-associated disorder (MOGAD), which are antibody-mediated demyelinating diseases with predilection for the optic nerves and spinal cord.[121] Pattern reversal visual evoked potentials (VEPs) may be performed to assess for abnormalities related to past or ongoing optic nerve demyelination, even among patients without any abnormal physical exam findings.[8]

Meningioma is most common in women of middle age. Proptosis may be a feature of a glioma. Brain MRI and/or head CT should be arranged for patients with proptosis.[120] With compressive lesions, venous drainage can become obstructed, resulting in a diagnostic triad of progressive visual loss, optic pallor, and optociliary shunts. An optociliary shunt is recognized on fundoscopy by large, tortuous vascular loops on the optic disk.[122] Severe headache, worse on coughing, and bilateral papilledema in a young woman, especially if obese, suggest idiopathic intracranial hypertension. An LP can be both diagnostic and therapeutic. The most effective treatment is weight loss.

In older adults with sudden and painless onset, ischemic optic neuropathy is the most frequent cause. Patients often have risk factors for microvascular disease such as hypertension, diabetes mellitus, hypercholesterolemia, and tobacco use. Screening with erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) is warranted when arteritis involvement is suspected (i.e., patient 50 years or older, presenting with temporal headache, visual disturbances, jaw or tongue claudication, fatigue, weight loss, malaise, or fever).[111] If ESR or CRP is elevated, high-dose corticosteroids should be started and a temporal artery biopsy arranged to confirm the diagnosis.[112] If tests for arteritis are negative and the

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history is not consistent with arteritic ischemic optic neuropathy, then a brain MRI should be considered to evaluate for unusual causes such as inflammatory disorders and mass lesions.[120]

In a patient with known systemic lupus erythematosus (SLE), Sjogren syndrome, granulomatosis with polyangiitis, or Behcet disease, ischemic optic neuropathy, or optic neuritis may develop, although these are rare causes and other eye conditions such as uveitis are more commonly associated. Symptoms may include red or dry eyes, itchy eyes, eye pain, or visual impairment. Patients may also have systemic symptoms of underlying disorders such as fever, malaise, arthralgia, myalgia, butterfly rash, anemia, or hematuria. If an underlying disorder is suspected, serology for ANA (SLE) or antineutrophil cytoplasmic antibody (granulomatosis with polyangiitis) should be performed. The Schirmer test can diagnose Sjogren syndrome, and pathergy testing is required for suspected Behcet disease. Optic nerve neuropathy should improve with treatment of the underlying condition.

Oculomotor (III), trochlear (IV), and abducens (VI)

Patients with third nerve palsy often present with paralysis of adduction, elevation, and depression of the eye. They usually have sudden-onset binocular horizontal, vertical, or oblique diplopia and a droopy eyelid. If a pupil is enlarged, the patient is frequently unaware. Isolated mydriasis is rarely caused by a third nerve palsy.

Acquired third nerve palsy can be further subdivided according to pupillary involvement and degree of extraocular muscle dysfunction into 3 types.[64]

- Normal pupillary function with complete ophthalmoplegia: cerebral angiography (to exclude an intracranial aneurysm) and brain MRI are not initially required, as the yield for a compressive lesion is very low.[123] [124] Observation is an appropriate diagnostic choice in older patients with vascular risk factors such as diabetes mellitus, hypertension, and smoking, as an ischemic nerve palsy is most likely. Patients who are over 50 years of age with third nerve palsy and intact pupillary function, and who have atherosclerotic risk factors, do not require brain imaging.[118] Patients may be followed up without further investigation for 6-8 weeks unless they have signs and symptoms suggesting arteritic ischemic neuropathy.[9] If symptoms resolve, then no further work-up is required. Any progression of symptoms or failure to resolve warrants neuroimaging with a brain MRI, and angiogram if MRI is negative.[9] Head CT and magnetic resonance angiography (MRA) are commonly used for screening purposes. Older patients with signs and symptoms suggesting arteritic involvement (headache, visual disturbances, jaw or tongue claudication, fatigue, weight loss, malaise, or fever) should have their ESR and/or CRP tested, and if these are abnormal a temporal artery biopsy is advised with presumptive treatment with high-dose corticosteroids.[9] Ocular myasthenia gravis may rarely mimic pupil-sparing third cranial nerve palsy; features include fluctuating fatigable ptosis or ophthalmoplegia.[125] [126] Recent use of sildenafil or cocaine may also account for ophthalmoplegia with normal pupillary function.[65] [66]
- Normal pupillary function with incomplete ophthalmoplegia: an MRI of the brain is needed to rule out a mass lesion. Cerebral angiography may be considered to rule out an intracranial aneurysm or vascular malformation such as a cavernous-carotid fistula.[9]
- Pupillary dysfunction with partial or complete ophthalmoplegia: the most worrying presentation and should be urgently evaluated.[127] Head CT and/or brain MRI is usually required.[118] [120] Any signs of neurologic deterioration warrant urgent head CT to rule out an intracranial mass lesion causing uncal herniation. Signs of meningismus, sudden severe headache, nausea and vomiting, and altered level of consciousness suggest subarachnoid hemorrhage.[9] [123] Migraines can also be consistent with headache, photophobia, and nausea, but consciousness is unimpaired and pupil function is

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not typically affected.[128] If abnormal pupillary function and partial or complete ophthalmoplegia is associated with fever, an LP should be performed to exclude meningitis. Signs suggesting a cavernous sinus thrombosis or mass include eye pain and headache, proptosis, chemosis, and ophthalmoplegia. There may also be sensory loss in the first 2 branches of the trigeminal nerve. Evaluation with gadolinium-enhanced brain MRI is advised. If head CT or brain MRI does not reveal a compressive lesion, a cerebral angiogram is needed to exclude a compressive intracranial aneurysm.[9] [123]

Trochlear (IV) nerve palsy is the most common cause of vertical diplopia. Patients often have a characteristic head tilt, away from the affected side, to reduce their diplopia. Abducens (VI) nerve palsy usually presents with horizontal diplopia and esotropia in primary gaze. Diagnosis of sixth nerve palsy involves excluding deficits in other cranial nerves, as truly isolated sixth nerve palsies are rare.[129]

In children <3 months old, congenital third nerve palsy is likely. All have some degree of ptosis and ophthalmoplegia, and most have pupillary involvement. A brain MRI is recommended to detect any associated brain anomalies.[130] Congenital lesions of the fourth and sixth nerves are very rare.

A history of head trauma may be elicited, but the mechanism is usually severe. The possibility of an underlying structural abnormality must be considered if a third, fourth, or sixth nerve palsy results from minor trauma, and neuroimaging is recommended.[77] [78] The fourth nerve is very susceptible to trauma due to its long intracranial course.

In younger patients, a thorough evaluation is warranted, including assessment of vascular risk factors and neuroimaging to rule out myriad structural causes, including base-of-brain tumors and aneurysm.[131] Brain MRI is the choice for imaging in cases without a definitive diagnosis.

Trigeminal (V)

This is the sensory nerve to the face and motor supply to the muscles of mastication. Any of its 3 main branches, ophthalmic (V1), maxillary (V2), or mandibular (V3), may be affected by a wide variety of etiologies. Urgent considerations to exclude are meningitis, skull-base osteomyelitis, herpes zoster infection, and cerebellopontine angle masses.

- Intra-axial nerve pathology is suggested by the presence of other neurologic deficits, which may include arm weakness, speech difficulties, or facial droop (due to seventh cranial nerve involvement). A sensory deficit on the opposite side of the body with ipsilateral facial anesthesia and loss of the corneal reflex may indicate lateral medullary (Wallenberg) syndrome. Isolated, sudden-onset sensory loss in the trigeminal distribution may represent pontine hemorrhage, and contrast-enhanced brain MRI is the best investigation. A trigeminal neuropathy may occur in the context of known MS, but it is rarely the presenting feature. Ipsilateral facial pain and temperature loss may be a feature of a high cervical spinal cord lesion at the C1/C2 level.
- Fever, headache, photophobia, nonblanching rash, stiff neck, or an altered level of consciousness may indicate meningitis. This requires urgent head CT imaging to exclude other serious pathology, such as subarachnoid hemorrhage, and an LP for CSF evaluation. Broad-spectrum antibiotics should be given presumptively, ideally after blood cultures have been taken.
- Otalgia, otorrhea, hearing loss, and headaches, with or without fever and trigeminal neuropathy, may indicate a diagnosis of skull-base osteomyelitis. Patients with these symptoms should undergo head CT or brain MRI to assess for bone destruction and soft-tissue changes.
- The presence of a herpetic rash in the V1 distribution needs a prompt ophthalmologic consult, as herpes ophthalmicus can lead to keratitis, corneal scarring, and visual loss. A recent history of herpes zoster may suggest a diagnosis of postherpetic neuralgia.

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- A history of trauma and acute onset of trigeminal neuropathy may indicate the presence of orbital, midface, mandibular, or skull-base fractures. Therefore, noncontrast thin section head CT is the best diagnostic tool. Electrodiagnostic (EDX) exam, including blink reflexes and needle electromyography (EMG) of the muscles of mastication, may be informative.[8] Additionally, symptoms in the V3 distribution and a history of oral surgery may suggest iatrogenic injury to the inferior alveolar nerve.
- Slowly progressive symptoms of trigeminal neuralgia may result from compression of the trigeminal nerve by a mass at the cerebellopontine angle.[81] Characteristic features of trigeminal neuralgia are paroxysmal, lancinating pain in the distribution of the trigeminal nerve, lasting a few seconds and often precipitated by specific triggers (e.g., touch, chewing).[132] The V2 and V3 divisions are the most commonly involved. These symptoms should be evaluated with high-resolution MRI (head, orbits, face, neck) without or with contrast.[119] Atypical facial pain is characterized by constant, deep pain of the face, but it may also localize to areas outside the trigeminal distribution; it is not caused by a trigeminal neuropathy. The cause is not known and it is considered a diagnosis of exclusion.[81]
- Symptoms of numbness with or without associated dysesthesia or paresthesia in the distribution of the trigeminal nerve may suggest an autoimmune cause.[87] [133] The neuropathy is usually purely sensory and eventually bilateral. Preservation of the jaw-jerk reflex with impairment of the other trigeminal reflexes is characteristic.[87] [133] Additionally, patients often have stigmata of the specific autoimmune disease. Appropriate diagnostic serology is recommended.
- Numb chin syndrome may occur due to metastasis to the mandible involving the mental nerve (a branch of the inferior alveolar nerve).
- Rarely, trigeminal dysfunction may be present from birth due to Chiari malformations or nerve aplasia. Chiari malformations may present with severe headaches (worse in the morning) or symptoms of syringomyelia such as pain and stiffness in the back and shoulders.
- Painful ophthalmoplegia of acute onset and boring in nature may be accompanied by paresthesias across the forehead (corresponding to the V1 division of nerve V), suggesting the rare Tolosa-Hunt syndrome (inflammation of the superior orbital fissure).

Facial (VII)

Presenting symptoms depend on the location of the lesion along the path of the facial nerve, but the most common is unilateral facial muscle weakness (1% to 2% may be bilateral), with or without associated facial and retroauricular pain, dysgeusia (distortion or loss of sense of taste), xerostomia (dry mouth), impaired salivation and lacrimation, and hyperacusis. It is important to determine whether a lesion is peripheral or central (a supranuclear or nuclear facial palsy). Central lesions generally spare the upper facial muscles and are often associated with additional neurologic findings, including contralateral limb weakness or altered mental status. Additionally, central facial palsies may spare emotional facial expression.[13]

- Central lesions are most frequently caused by contralateral cortical or ipsilateral pontine lesions, such as ischemic stroke or neoplasm. The presence of any of these additional signs should prompt immediate head CT or brain MRI.[134]
- A nuclear facial palsy may also result from a cerebral infarct or neoplasm involving the facial nucleus. Involvement of adjacent structures often results in additional neurologic findings, such as ipsilateral sixth cranial nerve (abducens) palsy or contralateral limb weakness.
- A history of trauma and the subsequent acute development of unilateral facial weakness and dysgeusia, without hyperacusis or reduced tearing, should be evaluated with a noncontrast thin section head CT of the skull base to assess for possible skull-base fracture just proximal to the origin of the chorda tympani.

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- Temporal bone fractures can also result in a seventh nerve palsy. EDX exam including facial motor nerve conduction studies (NCS) and EMG of the facial-innervated muscles in each branch of the facial nerve may be helpful but may be limited in the first 5 days of injury.[8] [32] Nerve ultrasonography of the facial nerve at the site of trauma can be beneficial, if the nerve is able to be visualized.
- Fever, headache, photophobia, nonblanching rash, stiff neck, or an altered level of consciousness may indicate meningitis. In the context of a coexistent seventh nerve palsy, this requires urgent head CT followed by an LP for CSF evaluation. Broad-spectrum antibiotics should be given presumptively, ideally after blood cultures have been taken.
- Sudden-onset headache associated with a cranial nerve palsy requires a head CT and LP to look for evidence of subarachnoid hemorrhage.
- Otalgia, otorrhea, retroauricular pain, and fever with seventh nerve neuropathy suggest middle ear or mastoid infection. There is frequently no fever, and white blood cell (WBC) count is generally normal, while ESR is markedly elevated. Suspicion for skull-base osteomyelitis should prompt radiologic evaluation with head CT and brain MRI.
- Acute progressive bifacial weakness may be seen in the setting of Guillain-Barré syndrome or its variants, either in conjunction with limb weakness, other cranial neuropathy, or in isolation. CSF evaluation and EDX studies should be strongly considered when Guillain-Barré syndrome is suspected, possibly with addition of neuroimaging and/or antibody testing.[114] Peripheral nerve ultrasonography can be helpful.
- Slowly progressive facial weakness with or without associated hearing loss or tinnitus generally points to a neoplastic etiology (such as schwannoma in the cerebellopontine angle, meningioma, or metastasis to the temporal bone). Brain MRI without and with contrast is recommended.[119] Surgical resection of such tumours can carry a risk of iatrogenic postoperative facial palsy, although intraoperative neuromonitoring can partially mitigate this risk.[135] [136]
- Patients with a history of tick exposure should be investigated for Lyme disease, especially in endemic regions. Unilateral or bilateral facial nerve palsy is a very early symptom in Lyme disease, and serologic testing is abnormal in 90% of patients with this infection.[90]
- A mass in the parotid region may be visible externally or palpable intraorally, and it may be increasing in size. This can put pressure on one or more branches of the facial nerve. Surgery to remove a parotid tumor also risks injury to the facial nerve. Referral to an otolaryngologist for evaluation and biopsy of any mass is recommended.
- In the absence of other neurologic findings, the most common causes of isolated facial nerve palsy are Bell palsy and Ramsay Hunt syndrome. A viral prodrome of symptoms of upper respiratory tract infection, myalgias, nausea and vomiting, diarrhea, and hypesthesia/dysesthesia in the region of the fifth cranial nerve may be present. Involvement of the facial nerve often progresses in a distal to proximal fashion, initially resulting in facial weakness (motor branch involvement), dysgeusia and reduced salivation (chorda tympani involvement), hyperacusis (stapedial branch involvement), and decreased tear production (geniculate ganglion involvement). Brain MRI is not usually indicated with isolated unilateral Bell palsy, although a high percentage of patients with Bell palsy show enhancement of the abnormal facial nerve after receiving gadolinium.[118] [119] [137] EDX studies, including direct facial motor NCS or EMG, may be performed at an early stage in the disease to aid in prognosis, but the usefulness of NCS in the first 5 days is limited.[138] Ramsay Hunt syndrome can be differentiated from Bell palsy by the concomitant presence of an erythematous herpetic rash of the ear or mouth, or by elevated serum varicella zoster virus (VZV) antibody titers or presence of VZV DNA.

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Vestibulocochlear (VIII)

Rapidly progressive vertigo (over several hours) with horizontal-torsional nystagmus is characteristic of vestibular neuritis. It is a self-limited condition that lasts for days and then slowly remits over several weeks.

Head thrusts and head heaves can be used to demonstrate "catch-up saccades," which tests for semicircular canal or utricle dysfunction. The head shake test involves tipping the head back by about 30° and shaking it from side to side quickly for 30 seconds. A unilateral vestibular defect causes slow nystagmus toward the side of the lesion. It is specific but not very sensitive. The Unterberger stepping test involves asking the patient to walk with his or her eyes shut and arms out in front. Rotation of more than 45° is abnormal, and usually this is toward the side of the lesion. Most patients recover completely. Associated symptoms may include nausea, vomiting, sweating, imbalance, disequilibrium, and unilateral hearing loss. Pure-tone audiogram is used to confirm and characterize hearing loss.

- A reduction in speech discrimination out of proportion to abnormalities on pure-tone audiogram suggests neural presbycusis.
- High-frequency sensorineural hearing loss and tinnitus that is bilateral and symmetric is consistent with damage from excessive noise or ototoxic drug. This includes aminoglycosides, platinum-based antineoplastic agents, salicylates, quinine, and loop diuretics.[102] Onset may be after only one dose of the offending drug or several months after exposure.
- Hearing loss in combination with tinnitus, vertigo, and disequilibrium may suggest a cerebellopontine angle mass. Tinnitus is often high pitched and ipsilateral to the side of the mass. Concomitant facial nerve palsy may also be present. Suspicion for a cerebellopontine angle mass should prompt brain MRI with gadolinium.[139] Surgical resection of such tumors can carry a risk of iatrogenic postoperative hearing loss, although intraoperative neuromonitoring can partially mitigate this risk.[135] [140]
- The presence of other neurologic deficits such as ipsilateral facial or contralateral limb weakness, contralateral temperature and pain loss, trigeminal sensory loss, or Horner syndrome should raise suspicion for a central cause.

Glossopharyngeal (IX) and vagus (X)

Isolated ninth cranial nerve neuropathy is rare, as lesions often result in tenth (vagus), eleventh (spinal accessory), or twelfth (hypoglossal) cranial nerve palsies due to the anatomical proximity to these nerves. Factors that help differentiate between specific etiologies include the duration since onset and a history of recent head or neck surgery.

- Iatrogenic injury to the recurrent laryngeal nerve is the most common single vagal nerve lesion and should be suspected when there is acute onset of vagal dysfunction after surgery (particularly thyroid, anterior cervical spine, and carotid endarterectomy). The left recurrent laryngeal nerve is more frequently injured than the right due to its longer course through the mediastinum.
- Fever, headache, photophobia, nonblanching rash, stiff neck, or an altered level of consciousness may indicate meningitis. In the context of a coexistent cranial nerve palsy, this requires urgent head CT followed by an LP for CSF evaluation. Broad-spectrum antibiotics should be given presumptively, ideally after blood cultures have been taken.
- Sudden-onset headache associated with a cranial nerve palsy requires a head CT and LP to look for evidence of subarachnoid hemorrhage.

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- A history of slowly progressive symptoms should raise suspicion of a compressive mass in the cerebellopontine angle (e.g., schwannoma), jugular foramen (e.g., glomus tumor), or parapharyngeal space (e.g., carotid body tumor). A glossopharyngeal neuroma located in the cerebellopontine angle may present with hearing loss (due to involvement of nerve VIII), while a neuroma located at the jugular foramen is likely to produce deficits in nerves IX through XI.[141] In this instance, head and/or neck CT or brain MRI with contrast should be obtained. Angiography may be considered for further evaluation of enhancing masses.
- Glossopharyngeal neuralgia is characterized by paroxysmal episodes of unilateral pain in the base of the tongue and deep neck, usually elicited by chewing or swallowing.[20] Potential causes include vessel loop or neoplastic compression, inflammatory or demyelinating disease,or rarely compression via an elongated styloid process (i.e., Eagle syndrome). Neuroimaging of the brainstem should be pursued for further evaluation.
- Trauma to the skull base may result in a ninth or tenth nerve palsy, but it is unlikely to be an isolated finding. If trauma is evident then a prompt thin section head CT of the skull base is recommended.
- Otalgia, otorrhea, hearing loss, and headaches may indicate skull-base osteomyelitis, but this rarely results in isolated ninth or tenth nerve palsy. There is frequently no fever, and WBC count is generally normal, while ESR is markedly elevated. These symptoms should prompt radiologic evaluation with head CT and brain MRI. Neck pain and fever might be due to a parapharyngeal space infection, and cervical spine CT with contrast should be obtained, with routine blood chemistries, CBC, and cultures.
- Vagus nerve enlargement can be seen in patients with Guillain-Barre syndrome, particularly in the most common form of acute demyelinating inflammatory polyradiculoneuropathy, with nerve ultrasonography at the carotid sheath. The nerve will lie adjacent to the carotid artery and jugular vein.[19] [142]
- A new onset of hoarseness with a long history of smoking is suspicious of an apical lung tumor impinging on the recurrent laryngeal branch of the tenth nerve. Chest radiograph or CT aids diagnosis. CT-guided or thoracoscopic biopsy may be required to establish the diagnosis. A history of cardiovascular disease, particularly left atrial enlargement or mitral stenosis, can cause impingement of the left recurrent laryngeal nerve in cardiovocal syndrome. Plain chest radiographs and chest CT can be helpful in making this diagnosis.

Spinal accessory (XI)

Injury to the spinal accessory nerve is rare and is most commonly a result of iatrogenic injury. A history of operative intervention, including neck dissection, cervical lymph node biopsy, carotid endarterectomy, jugular vein cannulation, and cosmetic rhytidectomy (face lift) is often elicited.[106] Blunt or penetrating trauma may also result in an isolated palsy.

The involvement of other lower cranial nerves may suggest an intracranial mass lesion. When lesions of the skull base are suspected, brain MRI with gadolinium enhancement is recommended.[27]

Typically, tumors of the jugular foramen and cerebellopontine angle extending into the foramen magnum or spinal cord also affect other cranial nerves. Three syndromes are recognized depending on the combination of cranial nerves involved:[108] [18]

- Vernet syndrome (neuropathy of IX, X, and XI)
- Collet-Sicard syndrome (neuropathy of IX, X, and XI, plus cerebellar disturbance)
- Villaret syndrome (neuropathy of IX, X, XI, and XII).

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Neuralgic amyotrophy may be mistaken for a spinal accessory mononeuropathy in view of restricted arm movements, including weak shoulder shrug and lateral scapular winging.[143] This is due to painful idiopathic inflammation of proximal branches of the brachial plexus, with resulting arm weakness or paralysis, and resolves slowly over time. EDX exam including spinal accessory motor NCS and EMG of the sternocleidomastoid (SCM) and/or trapezius muscles may be of benefit.[32]

Ultrasonography of the spinal accessory nerve in the posterior triangle of the neck can show focal nerve changes, such as nerve or isolated fascicular enlargement. Muscle ultrasonography of the SCM and/or trapezius muscles, including the upper, middle, and lower portions, may show atrophy and muscular changes with restricted dynamic motion of the muscles on activation.[144]

Hypoglossal (XII)

Causes can be nuclear or infranuclear. Additionally, motor neurone disease and progressive bulbar palsy (a bulbar form of amyotrophic lateral sclerosis) can result in dysfunction. EMG of the tongue is the most sensitive diagnostic test to detect denervation; however, muscle ultrasonography is the most sensitive diagnostic test to detect fasciculations.

- Fever, headache, photophobia, nonblanching rash, stiff neck, or an altered level of consciousness may indicate meningitis. In the context of a coexistent cranial nerve palsy, this requires urgent head CT followed by an LP for CSF evaluation. Broad-spectrum antibiotics should be given presumptively, ideally after blood cultures have been taken.
- Sudden-onset headache associated with a cranial nerve palsy requires a head CT and LP to look for evidence of subarachnoid hemorrhage.
- A history of slowly progressive symptoms raises suspicion for compression by a mass or tumor, and further evaluation with CT or MRI with contrast of the brain and/or neck is warranted. Dural arteriovenous fistulas and internal carotid artery aneurysms or dissections can present in the same way. Fistulas may present with headaches, pulsatile tinnitus, or stroke-like symptoms. If fistula is suspected, CT or conventional angiography is suggested.
- Patients with otalgia, otorrhea, hearing loss, and headaches with hypoglossal nerve dysfunction may have skull-base osteomyelitis. ESR is markedly elevated, and patients should be promptly evaluated with head CT and brain MRI.
- Fever and neck pain may indicate a neck abscess, and CT of the neck with contrast should be obtained.
- In a patient with a history of trauma and acute onset of nerve palsy, head CT (with fine cuts through the skull base to assess for skull-base fracture) or neck CT (if penetrating neck injury) should be obtained.
- Onset of hypoglossal palsy after neck irradiation or dissection should raise suspicion of iatrogenic injury.

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Differentials overview

Common

- Giant cell arteritis (II, III, IV, VI)
- Non-arteritic anterior ischemic optic neuropathy (II)
- Multiple sclerosis (II)
- Viral infection (II)
- Subarachnoid hemorrhage (III, IV, VI)
- Meningitis (III, IV, VI)
- Vascular malformations (V)
- Herpes zoster (V)
- Multiple sclerosis (V)
- Bell palsy (VII)
- Ramsay Hunt syndrome (VII)
- Ischemic stroke (VII)
- Vestibular neuritis (VIII)
- Neural presbycusis (VIII)
- Drugs (VIII)
- Iatrogenic (X)
- Apical lung tumor (IX, X)
- Iatrogenic (XI)
- Ischemic stroke (XII)

Uncommon

- Trauma (I)

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Uncommon

Neurodegenerative disorders (I)
Congenital (I)
CNS tumors (I)
Optic canal trauma (II)
CNS tumors (II)
Idiopathic intracranial hypertension (II)
Autoimmune disease: (e.g., systemic lupus erythematosus (SLE), Sjogren, granulomatosis with polyangiitis, Behcet disease [II])
Leber hereditary optic neuropathy (II)
Optical toxins or nutritional deficiency (II)
Neuromyelitis optica (II)
Uncal herniation (III, IV, VI)
Migraine (III, IV, VI)
Trauma (III, IV, VI)
Cerebral aneurysms (III, IV, VI)
Cavernous-carotid fistula (III, IV, VI)
Cavernous sinus thrombus (III, IV, VI)
CNS tumors (III, IV, VI)
Drugs (III, IV, VI)
Idiopathic intracranial hypertension (III, IV, VI)
Congenital (III, IV, VI)
Post-lumbar puncture (VI)
Meningitis (V)

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Uncommon

- CNS tumors (V)
- Autoimmune disorders (V)
- Skull-base osteomyelitis (V)
- Trauma (V)
- Dental abscess (V)
- Spinal cord lesion (V)
- Iatrogenic (V)
- Mandibular tumors (V)
- Congenital (V)
- Tolosa-Hunt syndrome (V)
- Wallenberg syndrome (V)
- Neurosarcoidosis (VII)
- CNS tumors (VII)
- Trauma (VII)
- Meningitis (VII)
- Iatrogenic (VII)
- Middle ear or mastoid infection (VII)
- Parotid tumor (VII)
- HIV associated (VII)
- Lyme disease (VII)
- CNS tumors (VIII)
- CNS tumors (IX, X)

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Uncommon

Parapharyngeal tumor (IX, X)
Meningitis (IX, X)
Skull-base osteomyelitis (IX, X)
Trauma (IX, X)
Parapharyngeal space infection (IX, X)
Eagle syndrome (IX)
Cardiovocal syndrome (X)
Trauma (XI)
CNS tumors (XI)
CNS tumors (XII)
Motor neurone disease/Progressive bulbar palsy (XII)
Chiari I and II malformations (XII)
Extracranial (tongue or neck) or skull-base tumors (XII)
Meningitis (XII)
Skull-base osteomyelitis (XII)
Parapharyngeal space infection (XII)
Trauma (XII)
Dural arteriovenous fistula (XII)
Internal carotid artery aneurysm or dissection (XII)
Iatrogenic (XII)

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Differentials

Common

Giant cell arteritis (II, III, IV, VI)

History	Exam	1st Test	Other tests
sudden and profound painless vision loss may have new onset headache, jaw claudication, proximal muscle weakness, anorexia and weight loss, incidence increases with age (more so at >80 years)	severe visual loss (often unable to see hand motions or worse), visual field defect, relative afferent pupillary defect, pale optic nerve swelling in affected eye with small optic nerve in fellow eye, optic nerve hemorrhages may be present; tenderness of scalp over temporal areas; abnormalities of the temporal, occipital, and facial arteries including thickening, tenderness, and nodularity; check for signs of involvement of extracranial arteries, such as bruits over the subclavian and axillary arteries	»**ESR:** Elevated Take blood for measuring ESR before starting a high-dose glucocorticoid, as inflammatory markers decrease once glucocorticoid therapy is started.[112] [148] [149] »**CRP:** elevated Take blood for measuring CRP before starting a high-dose glucocorticoid, as inflammatory markers decrease once glucocorticoid therapy is started.[112] [148] [149] »**FBC:** patients with GCA may have a normochromic, normocytic anemia with a normal WBC count and elevated platelet count; mild leukocytosis may occur Take blood for FBC before starting a high-dose glucocorticoid.[112] [149] »**vascular ultrasonography:** mural inflammatory changes in GCA If available, use rapid-access vascular	»**FDG-PET scan of head to mid-thigh:** mural inflammation or luminal changes of extracranial arteries in patients with suspected GCA; may demonstrate FDG uptake in the large vessels (aorta and major branches) in GCA A combined PET-CT scan using 18-fluorodeoxyglucose as a radioactive label can be used as an alternative to ultrasonography for the assessment of cranial and extracranial arteries in suspected GCA.[150] »**high-resolution MRI:** mural inflammation or luminal changes of cranial or extracranial arteries in patients with suspected GCA High-resolution MRI can be used as an alternative to ultrasonography for the assessment of cranial and extracranial arteries in suspected GCA.[150]

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Common

Giant cell arteritis (II, III, IV, VI)

History	Exam	1st Test	Other tests
		ultrasonography of the temporal and axillary artery first line to diagnose suspected GCA.[112] [148] [150] [151] »**temporal artery biopsy:** histopathology typically shows granulomatous inflammation in GCA Recommended by the ACR/EULAR as the definitive test for the diagnosis of GCA.[111] However, imaging is being increasingly used for diagnosis and vascular ultrasonography is the preferred early imaging test.[150] [151] For patients with suspected GCA, initially, a unilateral biopsy is recommended.[151] In addition, consider a temporal artery biopsy if expertise for ultrasonography is not available, or if the patient's pretest probability is high (typical features of GCA with elevated inflammatory markers) but the ultrasonography is normal.[112] Do not delay treatment while	

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Common

Giant cell arteritis (II, III, IV, VI)

History	Exam	1st Test	Other tests
		waiting for the biopsy to be performed.[112]	

◊ Non-arteritic anterior ischemic optic neuropathy (II)

History	Exam	1st Test	Other tests
sudden loss of part of visual field in one eye (often inferior eye); painless; may have headache; may be noted on waking; 75% of affected people are >50 years; history of phosphodiesterase type 5 inhibitor use for erectile dysfunction (which may potentially be associated with an increased risk of non-arteritic anterior ischemic optic neuropathy)	visual field defect; relative afferent pupillary defect; optic nerve swelling in affected eye with small optic nerve in fellow eye; optic nerve hemorrhages may be present	»**ESR:** normal Perform if patient is in the age range for giant cell arteritis (≥50 years). There are no other specific differentiating tests.	

◊ Multiple sclerosis (II)

History	Exam	1st Test	Other tests
woman 18-40 years old, acute, painful monocular visual loss, loss of color vision, sensory disturbances, tingling, numbness, weakness of limbs	afferent pupillary defect (asymmetric reaction to light when shined back and forth between the two eyes), normal fundus or mild optic disk edema, tremor, gait disturbance, limb weakness	»**MRI brain, cervical spine, and thoracic spine:** at least 2 areas of central demyelination	»**CSF:** positive for unpaired oligoclonal bands

◊ Viral infection (II)

History	Exam	1st Test	Other tests
child, recent viral infection or	triad of visual loss, swollen optic disk, and a macular star	»**none:** clinical diagnosis	

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Common

◊ Viral infection (II)

History	Exam	1st Test	Other tests
immunization, periocular pain			

Subarachnoid hemorrhage (III, IV, VI)

History	Exam	1st Test	Other tests
sudden-onset severe headache, neck pain, photophobia, nausea	may have altered level of consciousness, abnormal pupillary function	»**head CT:** blood in the subarachnoid space	»**LP:** xanthochromic CSF Performed if head CT is negative but clinical suspicion remains high.[113] »**cerebral angiography:** ruptured aneurysm Performed if subarachnoid hemorrhage is confirmed or if suspicion remains high but diagnosis cannot be confirmed by CT or LP.

Meningitis (III, IV, VI)

History	Exam	1st Test	Other tests
neck pain, stiffness, photophobia	nonblanching rash, may have additional cranial nerve deficits, altered level of consciousness, or fever; meningismus, positive Kernig and Brudzinski signs	»**head CT:** normal Performed to exclude an intracranial lesion. »**LP:** elevated cellular infiltrate, decreased glucose, elevated protein in CSF	»**Gram stain and cytology of CSF:** identification of bacterial cause

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Common

Vascular malformations (V)

History	Exam	1st Test	Other tests
most commonly unilateral, often progressive, paroxysmal, lancinating pain, lasts a few seconds to minutes, often precipitated by triggers (e.g., touch, chewing), commonly in V2 and V3 distributions	may have loss of sensation in the distribution of 1 or all trigeminal branches or weakness of the muscles of mastication	»**brain MRI:** aberrant vessel at the cerebellopontine angle These include the superior cerebellar artery or an unruptured intracranial aneurysm.	

◊ Herpes zoster (V)

History	Exam	1st Test	Other tests
3-4 days of burning or lancinating pain with or without vesicular rash in the distribution of ≥1 trigeminal nerve branches; postherpetic neuralgia: previous shingles infection, pain persisting despite resolution of rash	erythematous maculopapular rash followed by clear vesicles, rash does not cross midline	»**none:** clinical diagnosis	

◊ Multiple sclerosis (V)

History	Exam	1st Test	Other tests
known MS, advanced disease, woman 18-40 years old, acute painful monocular visual loss, loss of color vision, tingling, numbness, weakness of limbs	normal fundus or mild optic disk edema, tremor, gait disturbance, limb weakness	»**MRI brain, cervical spine, and thoracic spine:** demyelination in the pontine region	»**CSF:** positive for unpaired oligoclonal bands

◊ Bell palsy (VII)

History	Exam	1st Test	Other tests
acute onset of unilateral facial weakness, affects upper and lower face, may have history of viral prodrome	unilateral facial weakness involving the forehead, no other neurologic findings	»**none:** clinical diagnosis	

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Common

◊ Ramsay Hunt syndrome (VII)

History	Exam	1st Test	Other tests
sudden-onset (<72 hours) unilateral facial weakness (partial or complete), affects upper and lower face, severe ear and facial pain, vesicular lesions involving the pinna, possible hearing loss, tinnitus, or vertigo	parotid and/or neck masses, vesicular rash or blisters on the head, neck, and shoulders, cranial neuropathies (dermatomal rash, facial weakness, and ocular findings), presence of vesicles or blisters in the pinna and ear canal	»**none:** clinical diagnosis	»**varicella zoster virus (VZV) PCR:** positive for VZV DNA »**electromyography:** >90% decrease in amplitude of compound muscle action potential »**brain and cervical spine MRI with contrast:** stroke: lesion seen along the course of the facial nerve

Ischemic stroke (VII)

History	Exam	1st Test	Other tests
acute onset, possible contralateral limb weakness, dysphagia, dysarthria	sparing of upper facial muscles, may have decreased power of contralateral limbs, associated cranial nerve palsies, may have altered mental status	»**head CT:** may be normal; early ischemic change includes hypoattenuation (darkness) of the brain parenchyma Performed to exclude hemorrhagic stroke and to enable use of thrombolytic agents. CT head is the investigation of choice during initial evaluation of acute stroke, often in conjunction with CT angiogram. »**brain MRI with diffusion-weighted imaging:** acute ischemic infarct appears bright on diffusion-weighted imaging Used if CT is non-diagnostic or to better characterize the area of infarct.	

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Common

◊ Vestibular neuritis (VIII)

History	Exam	1st Test	Other tests
acute-onset vertigo over several hours, lasts days to weeks, slowly remitting, nausea, vomiting, sweating, imbalance, disequilibrium, occasionally unilateral hearing loss	horizontal-torsional nystagmus in primary gaze, worse with gaze deviation to opposite direction of slow phase of nystagmus, head thrusts; corrective saccades in direction of abnormality, past-pointing; deviation of arms to side of lesion; Unterberger stepping test: rotation to abnormal side	»**none:** clinical diagnosis	

◊ Neural presbycusis (VIII)

History	Exam	1st Test	Other tests
age-related, difficulty in speech discrimination, slow, gradual hearing loss, usually bilateral	normal otoscopic exam, Weber test may lateralize to least affected side	»**audiometry:** bilateral sensorineural hearing loss, usually high frequency	

Drugs (VIII)

History	Exam	1st Test	Other tests
new-onset vestibulocochlear nerve dysfunction after starting drug: aminoglycosides, platinum-based chemotherapeutic agents, salicylates, quinine, loop diuretics; tinnitus often bilateral and symmetric	Rinne test positive (normal air conduction > bone conduction), Weber test lateralizes to normal side, high-frequency hearing loss	»**audiometry:** progressive sensorineural hearing loss, beginning with the high frequencies	

◊ Iatrogenic (X)

History	Exam	1st Test	Other tests
recent thoracic or neck surgery, concomitant hoarseness	no palatal droop or uvula deviation	»**indirect laryngoscopy:**	»**flexible laryngoscopy:**

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Common

◊ Iatrogenic (X)

History	Exam	1st Test	Other tests
		ipsilateral vocal fold paralysis	ipsilateral vocal fold paralysis

Apical lung tumor (IX, X)

History	Exam	1st Test	Other tests
new-onset hoarseness, history of smoking, cough	auscultation: may hear decreased air entry, decreased percussion note, or normal	»**indirect laryngoscopy:** ipsilateral vocal fold paralysis Confirms involvement of recurrent laryngeal nerve. »**chest x-ray:** apical lung tumor	»**chest CT:** lung tumor and relationship to surrounding structures »**CT-guided or thoracoscopic biopsy:** malignant cells present

◊ Iatrogenic (XI)

History	Exam	1st Test	Other tests
isolated spinal accessory nerve palsy, recent lymph node biopsy, neck dissection, jugular vein cannulation, carotid endarterectomy, or cosmetic rhytidectomy (face lift)	weakness of sternocleidomastoid (SCM) and trapezius muscles, mild scapular winging	»**electromyography (EMG):** EMG of the SCM and/or trapezius muscles may reveal dysfunction and severity of injury »**nerve ultrasonography:** to assess for continuity of the spinal accessory nerve »**dynamic muscle ultrasonography:** muscle ultrasonography of the SCM and/or trapezius can be used to assess for atrophy, muscular changes, and restricted motion	

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Common

Ischemic stroke (XII)

History	Exam	1st Test	Other tests
acute onset, contralateral limb weakness, associated cranial nerve deficits; with progressive bulbar palsy: difficulty chewing, swallowing, or talking	tongue weakness, deviation to ipsilateral side on protrusion, atrophy, fasciculations, flaccidity; contralateral hemiplegia with facial sparing, contralateral loss of position and vibration sensation, sparing of pain and temperature	»**head CT:** may be normal; early ischemic change includes hypoattenuation (darkness) of the brain parenchyma Performed to exclude hemorrhagic stroke and to enable use of thrombolytic agents. CT head is the investigation of choice in acute stroke. »**brain MRI with diffusion-weighted imaging:** acute ischemic infarct appears bright on diffusion-weighted imaging Used if the diagnosis remains uncertain despite CT.	

Uncommon

Trauma (I)

History	Exam	1st Test	Other tests
temporal relationship to head trauma, occipital and side impacts most likely to cause olfactory loss	scar, may have other residual neurologic deficits	»**none:** clinical diagnosis	»**CT head:** may show previous skull fracture or resolving intracranial injury

◊ Neurodegenerative disorders (I)

History	Exam	1st Test	Other tests
Alzheimer disease: poor short-term memory, disorientation in time and place;	Alzheimer: difficulty performing familiar tasks; Parkinson: pill-rolling tremor	»**none:** clinical diagnosis	»**MRI brain:** normal scan with Parkinson, may show regional

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Uncommon

◊ Neurodegenerative disorders (I)

History	Exam	1st Test	Other tests
Parkinson: slow movement and rigidity, problems with posture and balance	most obvious at rest, increased tone, may have quiet or monotonous speech		brain atrophy with Alzheimer Clinicians should not necessarily obtain an MRI in adult patients with olfactory dysfunction who have no identifiable cause after a thorough history and physical exam (including nasal endoscopy), together with negative findings for preceding viral illness or head trauma.[118]

◊ Congenital (I)

History	Exam	1st Test	Other tests
isolated or associated with absent or incomplete puberty, dyspareunia, decreased libido, and erectile dysfunction or amenorrhea (Kallmann syndrome)	lack of secondary sexual characteristics, micropenis, lack of scrotal pigmentation, decreased muscle mass in Kallmann syndrome	»**MRI brain and olfactory bulbs:** hypoplastic olfactory bulbs Kallmann syndrome is hypoplasia of the olfactory bulbs in association with anosmia.	

CNS tumors (I)

History	Exam	1st Test	Other tests
early-morning headache, vomiting, ipsilateral anosmia, contralateral seizures, and altered level of consciousness (late signs)	optic atrophy and contralateral papilledema, ipsilateral central scotoma (Foster Kennedy syndrome)	»**MRI brain without and with gadolinium contrast:** space-occupying lesion impinging on the olfactory groove	

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Uncommon

CNS tumors (I)

History	Exam	1st Test	Other tests
		Frontal lobe tumors or meningiomas are most common.	

Optic canal trauma (II)

History	Exam	1st Test	Other tests
trauma to the outer brow or adjacent temporal bone	normal fundus or optic pallor after 3 to 4 weeks	»**facial/head CT:** optic canal fracture	

CNS tumors (II)

History	Exam	1st Test	Other tests
bilateral symptoms, progressive visual loss, signs of raised intracranial pressure; early-morning headache, vomiting, seizures and altered level of consciousness (late signs); meningioma: middle-aged woman; glioma: insidious visual loss, proptosis	optic pallor, optocilliary shunts; large tortuous vascular loops on optic disk, raised intracranial pressure; papilledema	»**brain MRI with contrast:** enhancing mass contiguous to the nerve, fusiform enlargement of the optic nerve or chiasm Optic nerve sheath meningiomas, optic nerve gliomas, sellar and parasellar masses (craniopharyngioma, meningioma, and pituitary tumors) can compress the optic nerve and chiasm.	

Idiopathic intracranial hypertension (II)

History	Exam	1st Test	Other tests
young woman, obesity, headache worse in the morning and on coughing or sneezing, nausea, vomiting, tinnitus, visual obscurations	bilateral papilledema, associated cranial nerve palsies of III, IV, VI	»**LP:** elevated opening pressure, but otherwise normal »**brain MRI:** normal Performed to exclude a space-occupying lesion	»**Goldmann perimetry:** constriction of visual fields May occur with long-standing raised intracranial pressure.

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Uncommon

Idiopathic intracranial hypertension (II)

History	Exam	1st Test	Other tests
		as a cause of raised intracranial pressure.	

◊ Autoimmune disease: (e.g., systemic lupus erythematosus (SLE), Sjogren, granulomatosis with polyangiitis, Behcet disease [II])

History	Exam	1st Test	Other tests
SLE: fatigue, weight loss, fever, anemia, arthralgia; Sjogren syndrome: fatigue, dry eyes, dry mouth; granulomatosis with polyangiitis: ocular symptoms of redness, pain, diplopia, cutaneous rash; Behcet disease: painful ulceration, impaired speech and balance, eye pain and blurry vision with CNS involvement	SLE: butterfly rash, photosensitive rash, oral ulceration; Sjogren: dental caries, corneal ulceration; granulomatosis with polyangiitis: proptosis, retinal hemorrhage/ exudate, skin lesions; Behcet: oral and genital ulceration, uveitis	»**ANA, double-stranded DNA, Smith antigen:** positive with SLE and Sjogren ANA is the best diagnostic test and is positive in virtually all patients with SLE. A positive ANA alone, however, is not diagnostic, as it may be positive in other connective tissue diseases, including Sjogren.[145] »**Schirmer test:** positive with Sjogren Quantitatively measures tears. A filter paper is placed in the lower conjunctival sac. The test is positive if <5 mm of paper is wetted after 5 minutes. »**antineutrophil cytoplasmic antibody (ANCA):** positive classic ANCA and protoplasmic-staining ANCA A positive ANCA test with clinical symptoms and signs is sufficient for diagnosis	

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Uncommon

◊ Autoimmune disease: (e.g., systemic lupus erythematosus (SLE), Sjogren, granulomatosis with polyangiitis, Behcet disease [II])

History	Exam	1st Test	Other tests
		of granulomatosis with polyangiitis. A negative ANCA test does not rule out the diagnosis. ANCA may also be positive with infections, other systemic inflammatory disorders, malignancy, and drug exposure. »**pathergy testing:** formation of a pustule within 48 hours A subcutaneous skin prick is performed using a 21-gauge sterile needle, usually in the forearm, and observed for the formation of a papule or pustule in 48 hours. Positive in up to 60% of patients with Behcet syndrome.	

◊ Leber hereditary optic neuropathy (II)

History	Exam	1st Test	Other tests
young man, may have maternal family history of optic neuropathy, acute visual loss in one eye, contralateral eye affected within weeks	optic disk pallor, decreased visual acuity, abnormalities of pupillary reflex	»**genetic studies:** specific mitochondrial point mutation Referral to clinical geneticist and mitochondrial DNA analysis is required.	

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Uncommon

◊ Optical toxins or nutritional deficiency (II)

History	Exam	1st Test	Other tests
exposure to ethambutol, infliximab, sildenafil, or amiodarone; tobacco use; deficiency of vitamins B1, B2, B9, and B12 due to famine or excessive ethanol; simultaneous bilateral symptoms, blurred central vision	central scotoma, color vision reduction; with nutritional cause: optic disk may be slightly hyperemic; with amiodarone: optic disk swelling and hemorrhage; with ethambutol: disk usually normal	»**treatment discontinuation:** resolution of symptoms »**vitamins B1, B2, B9, and B12 levels:** low »**Goldmann perimetry:** central scotoma and normal peripheral fields or symmetric field defects	

◊ Neuromyelitis optica (II)

History	Exam	1st Test	Other tests
typically middle-aged man or woman; visual loss in one eye, often followed by visual loss in the other eye after days to months; may or may not have history of myelitis	reduced visual acuity and reduced color vision ± brainstem syndrome, ± spasticity, weakness, or sensory disturbance in legs	»**MRI brain, cervical spine, and thoracic spine:** longitudinally extensive myelitis (>3 segments) ± brain demyelinating lesions	»**aquaporin 4 and myelin oligodendrocyte glycoprotein (MOG) antibodies (blood):** detection of antibodies

Uncal herniation (III, IV, VI)

History	Exam	1st Test	Other tests
sudden-onset nonpupil-sparing third nerve palsy, may have history of severe headache that is worse in the morning, nausea and vomiting	may have contralateral or ipsilateral hemiplegia with or without significant alteration in consciousness, ipsilateral pupillary dilation	»**head CT:** obliteration of the basal cisterns	

◊ Migraine (III, IV, VI)

History	Exam	1st Test	Other tests
prolonged headache, photophobia, nausea and vomiting, family history	no specific exam findings, temporary palsy of III, IV, or V resolves with resolution of migraine, pupil is not typically affected	»**none:** clinical diagnosis	

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Uncommon

Trauma (III, IV, VI)

History	Exam	1st Test	Other tests
acute head trauma or history of past head trauma with loss of consciousness	altered level of consciousness, associated residual focal neurology	»**head CT:** skull fracture, intracranial lesion	

Cerebral aneurysms (III, IV, VI)

History	Exam	1st Test	Other tests
can be asymptomatic, may have peripheral visual defect, loss of balance, coordination or speech problems	may have pupillary involvement, visual field defects	»**cerebral angiography:** aneurysm causing nerve compression Digital subtraction angiography or CT angiography most commonly performed.	

Cavernous-carotid fistula (III, IV, VI)

History	Exam	1st Test	Other tests
pulsatile tinnitus, progressive visual loss, proptosis, eye pain, history of trauma or connective tissue disease	pulsatile exophthalmos, chemosis, ocular bruit	»**CT or MRI of cavernous sinus:** cavernous-carotid fistula, enlargement of cavernous sinus, blockage of ophthalmic vein	»**cerebral angiography:** direct or indirect cavernous-carotid fistula

Cavernous sinus thrombus (III, IV, VI)

History	Exam	1st Test	Other tests
eye pain and unilateral headache, proptosis, chemosis, and ophthalmoplegia, may have periorbital edema	ptosis and mydriasis, papilledema and retinal vein dilation, decreased corneal reflex, may have sensory loss in skin supplied by first 2 branches of trigeminal nerve	»**gadolinium-enhanced brain MRI:** expansion of the cavernous sinuses, lateral convexity, increased dural enhancement; sphenoid sinus pathology may be present	

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Uncommon

Cavernous sinus thrombus (III, IV, VI)

History	Exam	1st Test	Other tests
		»**blood cultures:** septic cavernous sinus thrombosis; may have positive growth with a septic thrombosis	

CNS tumors (III, IV, VI)

History	Exam	1st Test	Other tests
craniopharyngioma in a child, acute loss of vision, macrocephaly, growth failure; in adults: insidious loss of vision, amenorrhea or erectile dysfunction	may have papilledema (with raised intracranial pressure), bitemporal hemianopia	»**brain MRI with contrast:** variable; T1 images show mixed solid and cystic components with enhancement of the solid component and cyst wall Pituitary or base-of-brain tumors are most common. »**visual fields testing:** variable, commonly bitemporal hemianopia if pressure on the optic chiasm	»**surgical biopsy and tissue histology:** adamantinous/ squamous epithelial tumor; calcification

◊ Drugs (III, IV, VI)

History	Exam	1st Test	Other tests
complete ophthalmoplegia, recent use of sildenafil or cocaine	normal pupil	»**none:** clinical diagnosis	

Idiopathic intracranial hypertension (III, IV, VI)

History	Exam	1st Test	Other tests
typically obese young adult woman with headaches, but no focal neurologic signs; bilateral visual loss	constriction of visual field due to papilledema	»**LP:** elevated opening pressure, but otherwise normal »**brain MRI:** normal	

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Uncommon

Idiopathic intracranial hypertension (III, IV, VI)

History	Exam	1st Test	Other tests
		Performed to exclude a space-occupying lesion as a cause of raised intracranial pressure.	

◊ Congenital (III, IV, VI)

History	Exam	1st Test	Other tests
<3 months old, present since birth	no specific associated features; if III affected: pupil involvement and ptosis	»**brain MRI:** may have associated intracranial abnormalities Congenital third nerve palsies are often associated with additional structural brain abnormalities.	

◊ Post-lumbar puncture (VI)

History	Exam	1st Test	Other tests
recent LP, transient symptoms of lateral gaze palsy	isolated lateral rectus palsy	»**none:** clinical diagnosis	

Meningitis (V)

History	Exam	1st Test	Other tests
neck pain, stiffness, photophobia	nonblanching rash, may have additional cranial nerve deficits, altered level of consciousness or fever; meningismus, positive Kernig and Brudzinski signs	»**head CT:** normal Performed to exclude an intracranial lesion. »**LP:** elevated cellular infiltrate, decreased glucose, elevated protein in CSF	»**Gram stain and cytology of CSF:** identification of bacterial cause

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Uncommon

CNS tumors (V)

History	Exam	1st Test	Other tests
most commonly unilateral, often progressive, paroxysmal, lancinating pain, lasts a few seconds to minutes, often precipitated by triggers (e.g., touch, chewing), commonly in V2 and V3 distributions	may have loss of sensation in the distribution of 1 or all trigeminal branches or weakness of the muscles of mastication	»**brain MRI:** tumor at the cerebellopontine angle Meningioma, schwannoma, epidermoid and arachnoid cysts, or malignant neoplasm.	

◊ Autoimmune disorders (V)

History	Exam	1st Test	Other tests
history of autoimmune disease, numbness with or without associated dysesthesias and paresthesias, often bilateral symptoms; SLE: fatigue, weight loss, fever, anemia, arthralgia; Sjogren syndrome: fatigue, dry eyes, dry mouth	impairment of trigeminal nerve reflexes, except jaw-jerk reflex (preserved); SLE: butterfly rash, photosensitivity, oral ulceration; Sjogren: dental caries, corneal ulceration	»**ANA, double-stranded DNA, Smith antigen:** positive ANA is the best diagnostic test and is positive in virtually all patients with SLE. A positive ANA alone, however, is not diagnostic, as it may be positive in other connective tissue diseases, including Sjogren and scleroderma. »**Schirmer test:** positive with Sjogren Quantitatively measures tears. A filter paper is placed in the lower conjunctival sac. The test is positive if <5 mm of paper is wetted after 5 minutes.	

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Uncommon

Skull-base osteomyelitis (V)

History	Exam	1st Test	Other tests
otalgia, otorrhea, hearing loss, headaches, neuropathic pain	loss of sensation in trigeminal distribution or weakness of the muscles of mastication	»**CBC:** usually normal WBC count »**ESR:** elevated »**head CT or brain MRI:** bone destruction, adjacent soft-tissue changes	

Trauma (V)

History	Exam	1st Test	Other tests
recent or remote history of trauma to orbit, midface, mandible, or skull base	crepitus over facial fracture site, inability to open jaw, malalignment of teeth; with skull-base fracture: Battle sign, periorbital ecchymosis, CSF rhinorrhea, bleeding from nose or ear	»**head CT (with fine cuts through region of interest):** orbital, midface, mandibular, or skull-base fracture	

◊ Dental abscess (V)

History	Exam	1st Test	Other tests
toothache, throbbing pain, possible loosening of tooth	pain exacerbated by tapping on top of tooth, gum recession, erythematous gum line	»**dental radiograph:** abscess under third molar tooth	

Spinal cord lesion (V)

History	Exam	1st Test	Other tests
symptoms of trigeminal neuralgia: unilateral, often progressive, paroxysmal, lancinating pain, lasts a few seconds to minutes, often precipitated by triggers (e.g., touch, chewing), commonly in V2 and V3 distributions	ipsilateral facial pain and temperature loss	»**cervical spine MRI:** spinal cord lesion at C1/C2	

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Uncommon

◊ Iatrogenic (V)

History	Exam	1st Test	Other tests
recent oral surgery before onset	loss of sensation in the distribution of the inferior alveolar nerve	»**none:** clinical diagnosis	

Mandibular tumors (V)

History	Exam	1st Test	Other tests
known extracranial tumor (e.g., nasopharyngeal carcinoma or neck malignancy with mandibular metastases)	unilateral chin or jaw numbness (numb chin syndrome)	»**mandibular MRI:** metastatic lesion to the mandible »**mandibular CT:** metastatic lesion to the mandible	

◊ Congenital (V)

History	Exam	1st Test	Other tests
Chiari I and II with syringomyelia: stiffness and pain in back and shoulders, facial pain, fatigue, severe headaches worse on straining, coughing, or sneezing	isolated or may include multiple cranial nerve neuropathies with Chiari I and II malformations	»**brain MRI; sagittal sections of the posterior fossa:** aplasia or hypoplasia of the fifth nerve; Chiari I and II (displacement >5 mm below the foramen magnum)	

◊ Tolosa-Hunt syndrome (V)

History	Exam	1st Test	Other tests
severe unilateral headache, acute-onset painful ophthalmoplegia, numbness across the forehead, diplopia, fatigue	mild proptosis, ophthalmoplegia, may have Horner syndrome	»**MRI brain and orbit with and without contrast:** inflammatory changes in the superior orbital fissure ± cavernous sinus, absence of intracranial mass	

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Uncommon

Wallenberg syndrome (V)

History	Exam	1st Test	Other tests
difficulty swallowing and speaking, ataxia, facial pain, vertigo	sensory impairment of trunk and limbs on contralateral side, and sensory and motor impairment of the face on the ipsilateral side, nystagmus, absent corneal reflex on ipsilateral side	»**brain MRI:** brainstem ischemia	

◊ Neurosarcoidosis (VII)

History	Exam	1st Test	Other tests
cloudy vision, diplopia, systemic involvement; fatigue, malaise, cough, shortness of breath	chorioretinal granulomas, swelling of optic nerve head with hemorrhage or elevation; systemic involvement: papilledema, fine inspiratory crackles on lung auscultation, lymphadenopathy, skin lesions	»**brain MRI:** diffuse or nodular enhancement around the optic nerve	»**lymph node or skin lesion biopsy:** noncaseating granulomas

CNS tumors (VII)

History	Exam	1st Test	Other tests
slowly progressive, hearing loss often present, may have tinnitus or hyperacusis, dysgeusia, and reduced tearing, contralateral limb weakness, ipsilateral sixth nerve palsy	weakness of both upper and lower facial muscles, ipsilateral sensorineural hearing loss, reduced power in contralateral limbs	»**brain MRI with gadolinium contrast:** compression from schwannoma, meningioma, or arachnoid or epidermal cyst in the cerebellopontine angle	

Trauma (VII)

History	Exam	1st Test	Other tests
recent trauma, dysgeusia	bruising and crepitus in temporal region, weakness of both	»**thin section head CT of skull base and/or temporal region:**	»**electromyography:** may reveal signs of nerve damage in facial

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Uncommon

Trauma (VII)

History	Exam	1st Test	Other tests
	upper and lower facial muscles, basal skull fracture; periorbital ecchymosis, Battle sign, CSF rhinorrhea, bleeding from nose or ear	skull-base fracture near the origin of the chorda tympani, temporal bone fracture	nerve-innervated muscles »**nerve ultrasonography:** used to assess for continuity at the site of trauma

Meningitis (VII)

History	Exam	1st Test	Other tests
neck pain, stiffness, photophobia	nonblanching rash, may have additional cranial nerve deficits, altered level of consciousness, or fever; meningismus, positive Kernig and Brudzinski signs	»**head CT:** normal Performed to exclude an intracranial lesion because of the presence of focal neurologic signs. »**LP:** elevated cellular infiltrate, decreased glucose, elevated protein in CSF Performed only if brain imaging excludes any contraindication.	»**Gram stain and cytology of CSF:** identification of bacterial cause

◊ Iatrogenic (VII)

History	Exam	1st Test	Other tests
temporal relationship to recent parotid gland surgery or otologic surgery (tympanoplasty, mastoidectomy, removal of exostoses)	paralysis of muscles supplied by one or more branches	»**none:** clinical diagnosis	

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Uncommon

◊ Middle ear or mastoid infection (VII)

History	Exam	1st Test	Other tests
otalgia, otorrhea, retroauricular pain	unilateral facial weakness, retroauricular cellulitis or swelling, often not febrile	»**otoscopy:** erythematous bulging tympanic membrane, fluid level behind membrane may be seen »**CBC:** WBC count usually normal »**ESR:** elevated	»**head CT or brain MRI:** bone destruction, adjacent soft-tissue changes

Parotid tumor (VII)

History	Exam	1st Test	Other tests
painless mass in the cheek, increasing size	may have regional lymphadenopathy, rarely blood or pus exudate from Stensen duct	»**fine needle aspiration:** may provide a histologic diagnosis Not routinely performed in all centers. May not be able to distinguish between benign and malignant lesions. »**parotid CT/MRI:** extent of tumor and relationship to local tissue planes, regional lymphadenopathy	»**electromyography:** may reveal nerve damage caused by tumor mass compression »**nerve ultrasonography:** used to assess for continuity at the site of trauma

◊ HIV associated (VII)

History	Exam	1st Test	Other tests
HIV-positive; fevers, night sweats, diarrhea	signs of HIV: lymphadenopathy, skin rashes, thrush infection, Kaposi sarcoma	»**HIV antibody test:** positive	

◊ Lyme disease (VII)

History	Exam	1st Test	Other tests
tick exposure, often bilateral facial	tick bite, bilateral facial weakness	»**Lyme serology:** elevated	

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Uncommon

◊ Lyme disease (VII)

History	Exam	1st Test	Other tests
weakness, preceding erythema migrans		Use a sensitive enzyme immunoassay (EIA) or immunofluorescence assay as a first test, followed by a western immunoblot assay for specimens yielding positive or equivocal results.[146] [147]	

CNS tumors (VIII)

History	Exam	1st Test	Other tests
hearing loss, ipsilateral high-pitched tinnitus, vertigo, disequilibrium, unilateral facial weakness; if VII involved: neurofibromatosis; bilateral symptoms possible	Rinne test positive (normal air conduction > bone conduction), Weber test lateralizes to normal side; involvement of VII: unilateral facial weakness	»**brainstem auditory evoked responses:** I-III peak latency prolongation Suggests lesion between pons and colliculus, most frequently vestibular schwannoma.	»**brain MRI:** mass lesion at the cerebellopontine angle The most common mass is a schwannoma arising from the vestibular division of the nerve. A history of neurofibromatosis may support this diagnosis. Other masses that can produce similar symptoms include meningiomas, arachnoid cysts, and epidermoid cysts.

CNS tumors (IX, X)

History	Exam	1st Test	Other tests
gradual development, other cranial nerves affected; with VIII: unilateral hearing loss or tinnitus; with IX: hoarseness, dysphagia, or dyspnea	IX; often asymptomatic, may have speech difficulty, problems swallowing or breathing	»**brain MRI with gadolinium:** nerve compression by mass at the cerebellopontine angle or jugular foramen	

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CNS tumors (IX, X)

History	Exam	1st Test	Other tests
		Cerebellopontine angle masses; schwannomas of the eighth or ninth nerve, meningiomas, arachnoid cysts, and epidermoid cysts can also cause compression, but other cranial nerves are often affected. Compression may also be caused by masses of the jugular foramen.	

Parapharyngeal tumor (IX, X)

History	Exam	1st Test	Other tests
neck or oropharyngeal mass, dysphagia or dyspnea, Eustachian tube dysfunction, hoarseness	painless palpable neck mass, thrill to auscultation if vascular	»**cervical spine CT or MRI with contrast:** parapharyngeal mass Localizes mass to prestyloid or poststyloid space, relationship to blood vessels and bone involvement demonstrated.	»**angiography:** variable, delineates relationship of tumor to major vessels; carotid body tumor: splaying of bifurcation May be considered if cervical spine CT demonstrates enhancing mass that is likely to be vascular.

Meningitis (IX, X)

History	Exam	1st Test	Other tests
neck pain, stiffness, photophobia	nonblanching rash, may have additional cranial nerve deficits, altered level of consciousness, or fever; meningismus, positive Kernig and Brudzinski signs	»**head CT:** normal Performed to exclude an intracranial lesion because of the presence of focal neurologic signs.	»**Gram stain and cytology of CSF:** identification of bacterial cause

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Meningitis (IX, X)

History	Exam	1st Test	Other tests
		»**LP:** elevated cellular infiltrate, decreased glucose, elevated protein in CSF Performed only if brain imaging excludes any contraindication.	

Skull-base osteomyelitis (IX, X)

History	Exam	1st Test	Other tests
otalgia, otorrhea, hearing loss, headaches, slurred speech, difficulty swallowing	dysarthria and weakness of palatal elevation associated with loss of sensation in trigeminal distribution, neuropathic pain, weakness of the muscles of mastication	»**CBC:** usually normal WBC count »**ESR:** elevated	»**head CT or brain MRI:** bone destruction, adjacent soft-tissue changes

Trauma (IX, X)

History	Exam	1st Test	Other tests
recent trauma, temporal relationship to nerve palsy, may have associated cranial nerve deficits	periorbital ecchymosis, Battle sign, CSF rhinorrhea, bleeding from nose or ear	»**head CT:** skull-base fracture	

Parapharyngeal space infection (IX, X)

History	Exam	1st Test	Other tests
possible neck pain, hoarseness, dysphagia	may have tenderness to neck palpation, fever	»**CBC:** elevated WBC count »**blood cultures:** may have positive growth »**cervical spine CT with contrast:** parapharyngeal mass/ abscess	

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◊ Eagle syndrome (IX)

History	Exam	1st Test	Other tests
paroxysmal unilateral pain at base of tongue and deep neck, elicited by chewing or swallowing	reproducible pain at base of tongue or deep neck with chewing or swallowing, palpable styloid possible	»**styloid CT:** elongated styloid process	

◊ Cardiovocal syndrome (X)

History	Exam	1st Test	Other tests
history of cardiovascular disease, hoarseness	no palatal droop or uvular deviation	»**indirect laryngoscopy:** left ipsilateral vocal fold paralysis	»**flexible laryngoscopy:** left ipsilateral vocal fold paralysis »**chest x-ray:** enlarged left atrium, enlarged aorta »**chest CT:** enlarged left atrium, enlarged aorta

Trauma (XI)

History	Exam	1st Test	Other tests
blunt or penetrating trauma to the neck	weakness of sternocleidomastoid (SCM) and trapezius muscles, mild scapular winging	»**CT cervical spine with contrast:** variable	»**Electromyography (EMG):** EMG of the SCM and/or trapezius muscles may reveal axonal injury »**ultrasonography:** Nerve ultrasonography of the spinal accessory nerve in the posterior triangle of the neck can show focal nerve changes, such as nerve or isolated fascicular enlargement; muscle ultrasonography of the SCM and/or trapezius muscles, including the upper, middle, and lower portions, may show atrophy and muscular changes with restricted dynamic

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Trauma (XI)

History	Exam	1st Test	Other tests
			motion of the muscles on activation

◊ CNS tumors (XI)

History	Exam	1st Test	Other tests
pain and decreased shoulder function; associated tenth nerve involvement: hoarseness, dysphagia	trapezius atrophy, drooping shoulder at rest; with tenth nerve involvement: palatal droop and uvula deviation	»**brain/cervical spine MRI with contrast:** foramen magnum, spinal cord, or jugular foramen lesion	»**nerve conduction studies:** prolonged latencies »**EMG:** signs of denervation

CNS tumors (XII)

History	Exam	1st Test	Other tests
acute onset, contralateral limb weakness, associated cranial nerve deficits; with progressive bulbar palsy: difficulty chewing, swallowing, or talking	tongue weakness, deviation to ipsilateral side on protrusion, atrophy, fasciculations, flaccidity; contralateral hemiplegia with facial sparing, contralateral loss of position and vibration sensation, sparing of pain and temperature	»**brain MRI with gadolinium:** medullary tumor	

Motor neurone disease/Progressive bulbar palsy (XII)

History	Exam	1st Test	Other tests
progressive symptoms, difficulty chewing, swallowing, or talking, muscle weakness in neck, arms or legs; respiratory weakness	tongue wasting, weakness, and fasciculations; nasal speech, reduced or absent gag reflex, drooling of saliva; sensory exam of cranial nerves and limbs normal	»**EMG of the intrinsic tongue muscles:** to assess for fibrillation, and fasciculation potentials; abnormal in motor neurone disease and progressive bulbar palsy	»**ultrasonography:** muscle ultrasonography of the intrinsic tongue muscles to assess for fasciculations (most sensitive)

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Uncommon

◊ Chiari I and II malformations (XII)

History	Exam	1st Test	Other tests
with syringomyelia: stiffness and pain in back and shoulders, facial pain, fatigue, severe headaches worse on straining, coughing, or sneezing	tongue weakness, deviation to ipsilateral side on protrusion (if unilateral), atrophy, fasciculations, flaccidity; frequent involvement of other cranial nerves	»**brain MRI; sagittal sections of the posterior fossa:** displacement >5 mm below the foramen magnum	

Extracranial (tongue or neck) or skull-base tumors (XII)

History	Exam	1st Test	Other tests
gradual development, common involvement of other cranial nerves	tongue weakness, deviation to ipsilateral side on protrusion, wasting, fasciculations, flaccidity	»**cervical spine CT/ MRI with contrast:** skull-base, neck, or tongue tumor Includes tumors and masses at the skull base, including metastatic tumors, meningioma, glomus jugulare tumor, chordoma, osteoma, sarcoma, nerve sheath tumors, epidermoid or dermoid cysts, arachnoid cyst, and carcinoma of the tongue or nasopharynx.	

Meningitis (XII)

History	Exam	1st Test	Other tests
neck pain, stiffness, photophobia	nonblanching rash, may have additional cranial nerve deficits, altered level of consciousness, or fever; meningismus, positive Kernig and Brudzinski signs	»**head CT:** normal Performed to exclude an intracranial lesion because of the presence of focal neurologic signs. »**LP:** elevated cellular infiltrate, decreased	»**Gram stain and cytology of CSF:** identification of bacterial cause

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Meningitis (XII)

History	Exam	1st Test	Other tests
		glucose, elevated protein in CSF Performed only if brain imaging excludes any contraindication.	

Skull-base osteomyelitis (XII)

History	Exam	1st Test	Other tests
otalgia, otorrhea, hearing loss, headaches	tongue weakness, deviation to ipsilateral side on protrusion, atrophy, fasciculations, flaccidity; often no fever	»**CBC:** usually normal WBC count »**ESR:** elevated	»**head CT or brain MRI:** bone destruction, adjacent soft-tissue changes

Parapharyngeal space infection (XII)

History	Exam	1st Test	Other tests
possible neck pain, fever; tenth nerve involvement: dysphagia and hoarseness	tongue weakness, deviation to ipsilateral side on protrusion; may have tenderness to neck palpation, fever	»**CBC:** elevated WBC count »**blood cultures:** may have positive growth »**cervical spine CT with contrast:** parapharyngeal mass/ abscess	

Trauma (XII)

History	Exam	1st Test	Other tests
recent or remote history of blunt head trauma or penetrating, gunshot, or stab wound to neck, acute onset of XII palsy	tongue weakness, deviation to ipsilateral side on protrusion, atrophy, fasciculations, flaccidity; entry wound, bleeding, other signs of head trauma, associated cranial nerve deficits, altered level of consciousness	»**CT head and neck:** basal skull fracture or soft-tissue neck trauma	

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Uncommon

Dural arteriovenous fistula (XII)

History	Exam	1st Test	Other tests
headache, pulsatile tinnitus, seizures, stroke	tongue weakness, deviation to ipsilateral side on protrusion, atrophy, fasciculations, flaccidity; vision disturbance, balance problems, hemiparesis, numbness and tingling, speech difficulty	»**cerebral angiography:** abnormal passage of dye between artery and vein	

Internal carotid artery aneurysm or dissection (XII)

History	Exam	1st Test	Other tests
history of trauma, neck manipulation, headache, dysarthria, ipsilateral neck pain	tongue weakness, deviation to ipsilateral side on protrusion; carotid bruit, Horner syndrome may be seen	»**cerebral angiography:** aneurysmal dilation or dissection	

◊ Iatrogenic (XII)

History	Exam	1st Test	Other tests
neck irradiation, carotid endarterectomy, or central line placement	tongue weakness, deviation to ipsilateral side on protrusion, atrophy, fasciculations, flaccidity	»**none:** clinical diagnosis	

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Online resources

1. NCBI: Leber hereditary optic neuropathy *(external link) (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0917796)*

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Figure 1 – BMJ Best Practice Numeral Style

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Contact us

+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
London
WC1H 9JR
UK

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Contributors:

// Authors:

James B Meiling, DO, RMSK

Assistant Professor
Department of Physical Medicine and Rehabilitation, Mayo Clinic, Rochester, MN
DISCLOSURES: JBM declares that he has no competing interests.

Tatsuya Oishi, MD

Assistant Professor
Department of Neurology, Mayo Clinic, Rochester, MN
DISCLOSURES: TO declares that he has no competing interests.

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// Peer Reviewers:

Benjamin D. Gallagher, MD, FACP

Assistant Professor of Medicine
Yale School of Medicine, New Haven, CT
DISCLOSURES: BDG declares that he has no competing interests.

Sabrina Ravaglia, MD, PhD

Staff Physician
Department of Neurological Sciences, Institute of Neurology C. Mondino, Pavia, Italy
DISCLOSURES: SR declares that she has no competing interests.